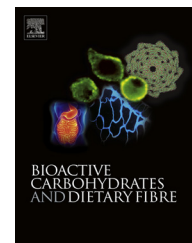


Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/bcdf

A review of bioactive plant polysaccharides: Biological activities, functionalization, and biomedical applications

Jun Liu*, Stefan Willför, Chunlin Xu*,¹

Process Chemistry Centre, c/o Laboratory of Wood and Paper Chemistry, Åbo Akademi University, Porthansgatan 3-5, FI-20500, Turku/Åbo, Finland

ARTICLE INFO

Article history:

Received 1 July 2014

Received in revised form

11 October 2014

Accepted 8 December 2014

Keywords:

Polysaccharides

Biological activity

Functionalization

Biomedical application

ABSTRACT

Natural polysaccharides from different sources have long been studied and widely used in different areas, such as food and feed, medicine and pharmaceuticals, and in papermaking. In recent decades, there has been an increased interest in the utilization of polysaccharides, particularly bioactive ones, for various novel applications owing to their biocompatibility, biodegradability, non-toxicity, and some specific therapeutic activities. The main goal of this paper was to review the sources, natively biological activities, isolation, characterization, and the structural features of natively bioactive polysaccharides. Moreover, the article has also been focused on the chemical/chemo-enzymatic functionalizations that may create novel opportunities to maximally exploit the various valuable properties of polysaccharides, particularly from wood species, in previously unperceived applications especially for biomedical applications, such as tissue engineering, wound healing, and drug delivery. This article was to review novel strategies to tailor functional materials with above mentioned application potentials for the polysaccharides from wood species.

© 2014 Elsevier Ltd. All rights reserved.

Contents

1. Introduction	32
2. Sources and biological activities of bioactive polysaccharides	32
2.1. Bioactive polysaccharides in dietary fibers	33
2.2. Bioactive polysaccharides in herbs	33
2.3. Bioactive polysaccharides in algae and lichens	33
2.4. Bioactive polysaccharides in wood	36
2.5. Bioactive polysaccharides from other sources	36
3. Isolation of bioactive polysaccharides	37
4. Functionalization of polysaccharides	37

*Corresponding authors. Tel.: +358 22154987.

E-mail addresses: jun.liu@abo.fi (J. Liu), swillfor@abo.fi (S. Willför), cxu@abo.fi (C. Xu).¹Tel.: +358 22154601.<http://dx.doi.org/10.1016/j.bcdf.2014.12.001>

2212-6198/© 2014 Elsevier Ltd. All rights reserved.

4.1.	Cellulose	40
4.2.	Hemicelluloses	41
4.2.1.	Xylans	42
4.2.2.	Galactomannans, glucomannans, and galactoglucomannans	42
4.2.3.	Xyloglucans	42
4.3.	Pectins	43
4.4.	Starch	45
4.5.	Chitin and chitosan	45
4.6.	Alginate	47
4.7.	Hyaluronic acid	48
5.	Structural analysis	49
6.	Biomedical applications	50
6.1.	Tissue engineering	50
6.2.	Wound healing and wound dressing	50
6.3.	Drug delivery and controlled release	51
7.	Concluding remarks and outlook	52
	Acknowledgements	52
	References	52

1. Introduction

Polysaccharides along with oligosaccharides, the most abundant group of biopolymers, have been found to participate in many biological processes, such as cell–cell communication, embryonic development, infection of bacteria and/or virus, and humoral and cellular immunity (Cooke, An, Kim, Solnick, & Lebrilla, 2007; Dube & Bertozzi, 2005; Varki, 1993). Therefore, polysaccharides together with polynucleotides, proteins, and lipids constitute the most important four biomacromolecules in life science. In this review, the bioactive polysaccharides refer to those polysaccharides that show biological effects on organisms and those polysaccharides that can be produced by living organisms or functionalized from sugar-based materials. Additionally, the biological effects that polysaccharides can exert are limited to therapeutic activities for diseases of humans and animals, and toxic activity responsible for causing human and animal disease (Colegate & Molyneux, 2008).

Although polysaccharides have been used for decades in various industrial applications, e.g. pharmaceuticals, biomaterials, food stuff and nutrition, and biofuels, growing understanding and deeper investigations of the importance of polysaccharides in life science are driving the development of polysaccharides for novel (biomolecular) applications (Alonso-Sande, Teijeiro-Osorio, Remunan-Lopez, & Alonso, 2009; Crini, 2005; García-González, Alnaief, & Smirnova, 2011; Kamberling & Boons, 2007; Pitarresi, Calabrese, Palumbo, Licciardi, & Giammona, 2009; Spizziri et al. 2010; Suh & Matthew, 2000). The biological activities of polysaccharides are strongly affected by their chemical structure and chain conformations. However, the macromolecular structures of plant cell wall polysaccharides, especially hetero-polysaccharides or so-called hemicelluloses, are extremely complex due to the presence of different monosaccharides as building blocks, which usually are isobaric stereoisomers, variations in sequence, linkage, branching, and distribution of side chains (An & Lebrilla, 2011; Cancilla, Penn, & Lebrilla, 1998; Mäki-Arvela, Salmi, Holmbom, Willför, & Murzin, 2011). Besides, the polysaccharides in microorganisms (fungi, yeasts, and bacteria), algae, plants, and animals are always physically and/or chemically tangled together with other

biomolecules, e.g. proteins, polynucleotides, lipids, lignin, and some inorganic mineral substances (Yang & Zhang, 2009). Therefore, comprehensive understanding the important roles of the bioactive polysaccharides in life science and exploring their application call for the multidisciplinary collaboration from experts on plant and microbial polysaccharides, glycochemistry, glycobiology, glycomedicine, phytology, and zoology (Colegate & Molyneux, 2008).

The aim of this article was to review the state-of-art in identification, isolation, functionalization, characterization, and application of bioactive polysaccharides derived from natural sources. Exploration of biomedical applications such as tissue engineering, wound healing, and drug delivery for polysaccharides were emphasized. The goal was to seek novel strategies to tailor functional materials with above mentioned application potentials for the polysaccharides from plants.

2. Sources and biological activities of bioactive polysaccharides

Polysaccharides can be classified in many possible ways, such as on the basis of structure, chemical composition, solubility, sources, and applications. With regard to the chemical composition, the polysaccharides are classified into two types, i.e. homo-polysaccharides or homoglycans, which are made up of a single type of monosaccharide, for example, cellulose and glycogen consist of glucose; hetero-polysaccharides or heteroglycans, which consist of more than one type of monosaccharide, such as heparin which consists of, α -L-idopyranosyluronic acid 2-sulfate and 2-deoxy-2-sulfoamino- α -D-glucopyranose 6-sulfate (Xiao et al., 2011). According to the glycosides linked onto the glycan, polysaccharides can also be classified as proteoglycans and glycoproteins, glycolipids, and glycoconjugates (Berg, Tymoczko, & Stryer, 2012; Gatti, Casu, Hamer, & Perlin, 1979). Based on the origins, bioactive polysaccharides from plant (dietary fibers, herbs and wood plants), algae and lichen, and other bioactive polysaccharides which are derived from animals (e.g. heparin, chondroitin sulfate, and hyaluronan)

and possess similar structural features (e.g. sulfate) as certain plant ones are reviewed in this paper. Specifically, the sources, chemical composition, molecular structure, and biological activities of naturally bioactive polysaccharides are reviewed below based on their original sources, to understand their presence and biological function.

2.1. Bioactive polysaccharides in dietary fibers

The dietary fiber was defined by the Food and Agriculture Organization (FAO) as a variety of indigestible plant polysaccharides including cellulose, hemicelluloses, pectins, oligosaccharides, gums, and various lignified compounds. Polysaccharides in the dietary fibers may be active in their native form or after chemical/enzymatic treatments. For example, the cellulose and hemicellulose can directly stimulate the bowel movement, while the inulin needs to be fermented into short-chain fatty-acids by microflora so as to prevent numerous gastrointestinal disorders (Pool-Zobel, 2005). Among the constituent in dietary fibers, polysaccharides play an important role in disease prevention. For example, pectins, inulin, and gums are able to slow the movement of food in the digestive tract, to reduce the blood cholesterol level, and to slow the speed of sugar absorption from the food into the blood, avoiding sudden hyperglycemia after food intake. Cellulose, hemicellulose and lignin constitute the insoluble fibers of dietary fibers which are able to stimulate the movement of bowel, speeding up the passage of waste through digestive tract, and to prevent constipation, diverticulosis, and hemorrhoids (Chawla & Patil, 2010; Tungland & Meyer, 2002). Numerous convincing epidemiological and clinical studies suggest that moderate or higher intakes of dietary fiber can effectively lower risks for developing diseases like diabetes (Weng, Lee, Yeh, Ho, & Pan, 2012), cardiovascular diseases including stroke (Casiglia et al., 2013), coronary heart disease and hypertension (Viuda-Martos et al., 2010; Whelton et al., 2005), hypercholesterolemia, hyperlipidemia (Chau, Huang, & Lin, 2004; Kendall, Esfahani, & Jenkins, 2010), obesity, and gastrointestinal (colorectal) cancer (Lunn & Buttriss, 2007). Generally, dietary fiber intake provides many benefits, including a decrease in intestinal transit time and an increase in stools bulk, and decreases in blood total cholesterol, and postprandial blood glucose, and/or insulin levels (Anderson et al., 2009; Brown, Rosner, Willett, & Sacks, 1999; Lunn & Buttriss, 2007).

Considering the importance of dietary fibers to human health and its specific working mechanism, we included the dietary fibers as a source of bioactive polysaccharides. The main sources, structure, composition, and biological effects of dietary fiber polysaccharides from follow-up investigations, intervention trials, and/or randomized-controlled trials are summarized in Table 1.

2.2. Bioactive polysaccharides in herbs

In traditional medicines of many countries, such as the traditional Chinese medicines, Japanese Kampo medicines, Indian Ayurveda, and Phyto-medicines in western countries, herbs have been used to treat various types of illnesses. Modern pharmacological experiments have identified that

the main or key components of herbal medicines generally include low-molar-mass compounds, such as alkaloids (e.g. phenanthridine alkaloid in *Lycoris radiata* herb, protoberberine alkaloids in *Rhizoma coptidis*), terpenoids (e.g. *Rabdosia* diterpenes and quassinoids), flavonoids (e.g. *scutellaria* flavones), saponins; and high-molar-mass proteins, tannins, and most importantly polysaccharides (Tang, Hemm, & Bertram, 2003a,b). Of these fractions in herbal medicines, polysaccharides have been identified as one of the major active ingredients responsible for various pharmacological activities, such as immunostimulatory activity, antiviral activity, antioxidant activity, antitumor activity, radioprotection effect, hepatoprotection effect, and antifatigue effect. (Harlev, Nevo, Lansky, Ofir, & Bishayee, 2012; Jin, Huang, Zhao, & Shang, 2013; Li & Peng, 2013; Thakur et al., 2012; Tian, Zhao, Guo, & Yang, 2011). Polysaccharides in various herbs are believed to be active in their native form to stimulate human immune systems, to inhibit viral replication, to scavenge free radicals, and to inhibit lipid oxidation (Harhaji Trajkovic et al., 2009; Ke et al. 2011; Li & Peng, 2013). A brief summary of the recent advances in the study and application of bioactive polysaccharides from herbal medicines for disease control and treatment is presented in Table 1.

2.3. Bioactive polysaccharides in algae and lichens

The polysaccharides in algae and lichens have attracted an increasing interest due to their excellent physical properties, such as thickening, gelling, and stabilizing ability, and also due to their beneficial biological activities, such as anticoagulant, antithrombotic, antioxidative, antiviral, anti-inflammation, antitumour, and immunomodulating activity. (Kim & Li, 2011; Olafsdottir & Ingólfsdottir, 2001).

The sulfated polysaccharides are one group of the most interesting and attractive components in the marine algae, such as fucoidans and laminarans in brown algae (*Phaeophyceae*), carrageenans in red algae (*Rhodophyceae*), and ulvans in green algae (*Chlorophyceae*) (Wijesekara, Pangestuti, & Kim, 2011). Anticoagulant activity could be the most attractive property of the sulfated polysaccharides. For example, the sulfated galactans (carrageenan) from red algae and the sulfated fucoidans from brown algae have been identified with high anticoagulant activity. Sulfated polysaccharides from algae were reported to possess similar or even stronger activity than those of heparin (Maeda, Uehara, Harada, Sekiguchi, & Hiraoka, 1991). There are several other beneficial biological activities of sulfated polysaccharides from algae that have also been intensively studied. For example, (1) the highest antioxidant activity expressed as protection of the human body against damage from reactive oxygen species was found in fucoidan (followed by alginate and laminaran); (2) the anticancer activity of the algae was found to originate from its free-radical scavenging and antioxidant activity (Chattopadhyay et al., 2010); (3) the antiviral activity of carrageenans, fucoidans, and sulfated rhamnogalactans was proved by exerting inhibitory effects on the entry of herpes and HIV viruses into cells (Wijesekara et al., 2011); (4) immunomodulatory activity of algae-derived polysaccharides was shown by enhancing the phagocytic and secretory activity of

Table 1 – A brief summary of bioactive polysaccharides from different sources.

Type	Name	Composition	Sources	Physiological effects	Ref.
Dietary fiber	Cellulose	β -(1→4) linked-D-glucopyranose, linear and homopolysaccharides	Grains, fruit, vegetables, nuts	Increase stool bulk and help to regulate bowel movement	Viuda-Martos et al. (2010)
	Hemicelluloses	Four classes of structurally different cell-wall polysaccharides including xylans, mannans, β -glucans with mixed linkages and xyloglucans	Vegetative and storage tissues of annual and perennial plants, fruit, legumes, and nuts	Immunomodulating activity, antithrombotic activity, free radicals eliminating activity, antioxidant activity, bowel movements regulating and cholesterol lowering effect	Doliška et al. (2012), Ebringerová et al. (2008), Heinze (2005), Mudgil and Barak (2013), Wu and Chen (2011)
	Pectins	α -(1→4)-D-Galacturonic acid and rhamnose backbone, arabinose, galactose, xylose side chains, partially O-methyl/acetylated	Plant primary cell wall, soft tissues of fruit and vegetable	Intestinal immune system modulating activity, cholesterol lowering effect, decrease gastric emptying and small intestine transit time	Mudgil and Barak (2013), Suh et al. (2013), Yu, Kiyohara, Matsumoto, Yang, and Yamada (2001)
	β -Glucans	β -(1→4)-D-Glucose and β -(1→3)-D-glucose	Oats, barley grains	Cholesterol lowering effect, control of blood glucose level and lipids; reduction of hypertension, stimulation of immune system	Charlton et al. (2012), Chen and Raymond (2008), Marques, Dhont, Sorgeloos, and Bossier (2006), Wolever et al. (2011)
	Resistant starch	α -(1→4) and/or (1→6) linked D-glucopyranosyl	Cooked and cooled potatoes, rice, green bananas, legumes, food containing modified starch	Prevention of colonic cancer, hypoglycemic and hypocholesterolemic effects, role as prebiotic, inhibition of fat accumulation, enhance the absorption of minerals	Bird, Conlon, Christophersen, and Topping (2010), Fuentes-Zaragoza, Riquelme-Navarrete, Sánchez-Zapata, and Pérez-Álvarez (2010)
	Gums	Galactan, xylan, xyloglucan, glucuronic mannan, galacturonic rhamnosan type	Locust bean gum, gum arabic, and guar gum which are exudates of trees or isolated from seeds	Hypocholesterolemic and hypotriglyceridemic effects, influence on postprandial glycemia, lipemia, and lipoprotein composition, gel-forming to increase satiety, slow gastric emptying	Chawla and Patil (2010), Whistler and BeMiller (1993)
	Inulin	β -(1→2)-D-Fructofuranosyl	Chicory root, wheat, onion, garlic	Hypolipidemic effects, prebiotic properties which influence gut microbiota, stimulate mineral (calcium, magnesium) absorption	Capriles and Areas (2013), Cherbut (2002), Russo et al. (2012)
Herbs	Konjac glucomannan	β -(1→4)-Linked D-glucose and β -(1→4)-linked D-mannose	Amorphophallus konjac plant	Cholesterol lowering, bulking for weight reduction, reduces the risk of constipation	Al-Ghazzewi et al. (2007)
	Ginseng polysaccharides	(1→4)-Linked homogalacturonan backbone. (1→2(3))-Linked rhamnose on position 4 as a part	Ginseng, the root of <i>Panax ginseng</i>	Antitumor activity	Baek et al. (2010)

Table 1 (continued)

Type	Name	Composition	Sources	Physiological effects	Ref.
Algae and lichens	<i>Astragalus</i> polysaccharides	of backbone or ramified regions. (1→5(2))-Linked arabinose with branch points at position 3. (1→3(4))-Linked terminal galactose α -(1→4)-D-Glucan with α -(1→6)-branches	<i>Astragalus</i> roots	Immunomodulating activity, antiviral activity	Li et al. (2011), Li and Peng (2013)
	<i>Acanthopanax senticosu</i> polysaccharides	Seven monosaccharides including rhamnose, xylose, glucose, mannose, arabinose, galactose, and glucuronic acid in a molar ratio of 7.45:18.63:25.15:0.93:8.35:2.79:5.69	<i>Acanthopanax senticosu</i> leaves	Antioxidant and immunobiological activity	Chen et al. (2011)
	<i>Polygonum multiflorum</i> Thunb polysaccharides	Mainly glucose	<i>Polygonum multiflorum</i> Thunb root	Antioxidant activity and antiglycation	Lv, Cheng, Zheng, Li and, Zhai (2014)
	<i>Platycodon grandiflorum</i> polysaccharides	(1→4(6))-Linked galactopyranosyl residues, with branches attached to O ₃ of (1→6)-linked galactose residues. Arabinose and galactose in the molar ratio of 1.42:1.0	<i>Platycodon grandiflorum</i> root	Antiangiogenic activity	Xu, Dong, Qiu, Cong, and Ding (2010)
	Green algae sulfated polysaccharides	(1→3(6))-Linked galactose, (1→3(4))-linked arabinose, (1→4)-linked glucose and terminal, (1→4)-linked xylose residues. Sulfations occur on O ₆ of galactose and O ₃ of arabinose. Sulfate ester content: 9%	Green algae, <i>Caulerpa racemosa</i>	Antiviral activity (herpes simplex virus type 1 and 2)	(Ghosh et al., 2004)
	Brown algae sulfated polysaccharides	Fucan: (1→3)-linked α -L-fucopyranosyl backbone, mostly sulfated at C ₄ , and branched at C ₂ with non-sulfated fucufuranosyl and fucopyranosyl units, and 2-sulfated fucopyranosyl units. Galactan: D-galactopyranose units linked on C ₃ and C ₆ , and sulfation mostly on C ₄ . Sulfate ester content: 30–34%/21–24%	Brown algae, <i>Adenocystis utricularis</i>	Antiviral activity (herpes simplex virus type 1 and 2), Antiretroviral activity (HIV-1)	Ponce, Pujol, Damonte, Flores, and Stortz (2003), Trincherro et al. (2009)
	Red algae sulfated polysaccharides (porphyran)	Backbone of alternating β -(1→3)-linked D-galactosyl units and α -(1→4)-linked L-galactosyl, (1→6)-sulfate or 3,6-anhydro- α -L-galactosyl units. Sulfate ester content: 17%	Red algae, <i>Porphyra haitanensis</i>	Antioxidant activities, anticoagulant activities	Zhang et al. (2010)
	Green algae sulfated rhamnan	(1→2)-Linked L-rhamnose residues with sulfate groups substituted at positions of C ₃ and/or C ₄ . Sulfate ester content: 23%/25%	Green algae, <i>Monostroma latissimum</i>	Anticoagulant activity	Li et al. (2012a), Mao et al. (2009)
	Algal fucoidan	Fucose, galactose. Sulfations occur on position-2 and -3. Sulfate ester content: 41–92%	Brown algae, <i>Ecklonia cava</i>	Anti-inflammatory activity	Kang et al. (2011)
	Brown algae sulfated polysaccharides	Mainly composed of fucose (82%), galactose (14%), and small amounts of xylose and mannose. Sulfate ester content: 92% Galactofuranomannans, β -glucan lichenan Galactofuranomannans, β -glucan	Brown algae, <i>Ecklonia cava</i> Lichen <i>Thamnolia vermicularis</i> var. <i>subuliformis</i>	Antiproliferative activity, anticancer activity Immunomodulating activity	Athukorala et al. (2009) Omarsdottir, Freysdottir, and Olafsdottir (2007)

Table 1 (continued)

Type	Name	Composition	Sources	Physiological effects	Ref.
β-Glucans lichenan	Lichenan: β-(1→3 (4))-linked glucan Isolichenan: α- (1→3(4))-linked glucan Pustulan: β-(1→6)-linked glucan partially acetylated at O ₃ Heteroglycan	Lichens, <i>Cetraria islandica</i> / <i>Umbilicaria proboscidea</i> / <i>Thamnolia</i> <i>vermicularis</i> var. <i>subuliformis</i> / <i>Peltigera canina</i>		Immunomodulating activity	Omarsdottir, Olafsdottir, and Freysdottir (2006)
Other sources (derived from animal)	Heparan sulfate/ heparin	(1→4) Linked glucuronic/ iduronic acid and N- acetylglucosamine disaccharide unites with variable 2/3/6-O- sulfonation	Animal granules of mast cell (heparin); Animal tissues, e.g. porcine intestine, bovine lung	Anticoagulant activity	Linhardt (2003), Schedin-Weiss et al. (2008)
	Chondroitin sulfate/dermatan sulfate	(1→3) linked glucuronic/iduronic acid and (1→4) linked N- acetylgalactosamine disaccharide unites with variable 2/3/6-O-sulfonation	Animal cartilaginous tissue, e.g. bovine trachea, and shark cartilage	Modulating cellular growth and signaling, maintaining the extracellular matrix integrity	Barnhill et al. (2006), Hitchcock, Costello, and Zaia (2006), Takegawa et al. (2011)

macrophages and by inducing the production of reactive oxygen species, nitric oxide, and cytokines (Schepetkin & Quinn, 2006).

Polysaccharides isolated from lichens are primarily linear or scarcely substituted α- and/or β-glucans. Such glucans from lichens have been reported to possess a variety of biological activities like antitumour activity, immunomodulating effect, and antiviral activity (Olafsdottir & Ingólfssdottir, 2001; Omarsdottir, Freysdottir, & Olafsdottir, 2007; Zambare & Christopher, 2012). The β-glucans from lichens and lichenan showed the immunomodulating activity by stimulating a wide range of immune responses such as cytokine release, generation of reactive oxygen species and nitric oxide, and release of arachidonic acid metabolites (Schepetkin & Quinn, 2006). Lichenan with a galactoglucomannan structure showing anticoagulant and antithrombotic activity was also reported (Martinichen-Herrero, Carbonero, Sassaki, Gorin, & Iacomini, 2005).

Biological activities of the sulfated polysaccharides from both algae and lichens highly depend on their structural features, such as the sulfate content and distribution of sulfate groups on the main chain, molar mass, and stereochemistry. Therefore, modification of the native sulfate polysaccharides to obtain the bioactive polysaccharides with desired molecular size and functional property for application is needed (Ngo & Kim, 2013; Wijesekara et al., 2011). A brief summary of recent research advance is listed in Table 1.

2.4. Bioactive polysaccharides in wood

Polysaccharides from wood mainly include cellulose and a few primary groups of hemicelluloses, i.e. xylans, glucanans, arabinans, galactans, and glucans (Fraser-Reid, Tatsuta, & Thiem, 2008; Gatenholm & Tenkanen, 2004; Heinze, 2005). Galactoglucomannans and pectins from wood have been reported to show immunostimulating activities and radical-scavenging activities (Ebringerová et al., 2008; Le Normand et al., 2014). Xylans or Xylooligosaccharides from hardwood, softwood, and dietary fibers have also been found to possess great prebiotic potential for application in both medical and

nutrition research (Aachary & Prapulla, 2011). However, most polysaccharides do not show biological activity unless some modifications are carried out. Cellulose derivatives, such as methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose, have found promising applications in various fields such as food, medical, pharmaceutical, and cosmetics (Li & Mei, 2006). Therefore, further review of wood polysaccharides will be presented in the later functionalization/modification section. There, the strategies to functionalize wood polysaccharides towards bioactive applications will be discussed in detail.

2.5. Bioactive polysaccharides from other sources

The sulfated glycosaminoglycans such as the heparan sulfate (HS), chondroitin sulfate (CS), dermatan sulfate (DS), and keratin sulfate represent another group of bioactive polysaccharides that are mainly derived from animals. HS chains are made up of variably sulfated and N-acetylated repeating disaccharide unites, i.e. glucuronic/iduronic acid and glucosamine (Chappell & Liu, 2013; Linhardt, 2003; Sakiyama-Elbert, 2014). Heparin, the most highly sulfated heparan sulfate, has been widely used as the most effective clinical anticoagulant. Anticoagulant activity of the heparin highly relies on its specific structure sequence, within which the binding site of an important protein (antithrombin III) is crucial for heparin to prevent the generation of a fibrin clot which is formed by the action of thrombin (Schedin-Weiss, Richard, Hjelm, & Olson, 2008). Understanding of this structure–activity relationship of heparin offers the opportunity to develop drugs with higher specificity and better regulation of coagulation and to explore other therapeutic applications such as infection, inflammation, cancer and wound-healing treatment (Linhardt, 2003; Rajangam et al., 2006; Sakiyama-Elbert, 2014; Zhang et al., 2013a; Zhang, Wardwell, & Bader, 2013b). CS/DS chains are composed variably sulfated N-acetylgalactosamine and glucuronic acid or its epimeride iduronic acid disaccharides repeating units (Silbert & Sugumaran, 2002; Takegawa et al., 2011). Growing research evidence reveals the previously less or

unperceived functions of CS/DS (Sugahara et al., 2003), for example being a key molecule of the brain extracellular matrix (Kwok, Warren, & Fawcett, 2012), regulating the cell adhesion, proliferation and migration during wound healing (Zou et al., 2004), signaling of growth factor in skeleton (Alliston, 2010).

Hyaluronic acid (HA), which is mainly derived from animal and plant tissues, is a linear non-sulfated glycosaminoglycan with repeating disaccharide units of β -(1 \rightarrow 4)-D-glucuronic acid and β -(1 \rightarrow 3)-N-acetyl-D-glucosamine. HA is an essential component of the extracellular matrix, mediating cellular signaling, wound repair, morphogenesis, and matrix organization and thus HA and its derivatives have been clinically used for medical applications, such as viscosupplementation, eye surgery, and drug delivery for decades (Balazs, 2009; Gaffney, Matou-Nasri, Grau-Olivares, & Slevin, 2010; Prestwich, 2011).

Chitin, the second most abundant polymer after cellulose, is a co-polymer of β -(1 \rightarrow 4)-linked N-acetyl-glucosamine (acetylated unit) and N-glucosamine (deacetylated unit) which randomly distributed along the chain (Khan & Ahmad, 2013). Chitin can primarily be found in the exoskeleton of arthropods (e.g., shells of crabs and shrimp) and in the cuticles of insects, however it have been identified and extracted in the cell walls of fungi and yeast (Bartnicki-Garcia, 1968; Logesh, Thillaimaharani, Sharmila, Kalaiselvam, & Raffi, 2012). So the chitin and chitosan will be also reviewed in this paper even if there are not belonging to the plant kingdom. Partial deacetylation of chitin under alkaline conditions or by chitin deacetylase yields the most important derivative of chitin, i.e. chitosan. Generally, when the number of N-glucosamine units is higher than 50%, the term chitosan is used (Fig. 4) (Khor & Lim, 2003). Oligomers from partial acid hydrolysis of chitin and chitosan were recognized for their bioactivity, including hemostatic action, anti-inflammatory effect, antitumoral, antibacterial, and fungicidal properties, eliciting chitinase, and regulating plant growth (Rinaudo, 2008).

3. Isolation of bioactive polysaccharides

Generally, (bioactive) polysaccharides are present together with various other components such as proteins, polynucleotides, lipids, extractives, lignin, and some inorganic mineral substances. However, the desired biological activities of the naturally bioactive polysaccharides may be undermined by other compounds, which may even cause antagonistic effects or undesirable toxicity. In other words, pure bioactive polysaccharides could enable the safe, reproducible and accurate dosage for experimental or therapeutic applications, and also enable the investigation of structure/activity relationship, facilitating the development of new compounds with similar or higher desirable bioactivities (Colegate & Molyneux, 2008). Thus, the isolation of natural polysaccharides that have biological activities toward organisms from various sources plays an important role in the investigation and application of bioactive polysaccharides.

Generally, bioactivities of polysaccharides are highly dependent on their structural information, such as molar mass, extent of side chains/groups or substitution and their distribution on the backbone. Thus, how to isolate the polysaccharides from the complex matrix networks, meanwhile minimizing any loss of the desired bioactivity, is one of the most important tasks to deal with.

In recent years, novel and effective extraction methods, such as supercritical fluid extraction, microwave-assisted extraction, and the most promising hot-water extraction, have gained increasing attention due to their environmentally friendly process, higher extraction efficiency, cost effectiveness, and structure-preservation ability (Chao, Ri-fu, & Tai-qi, 2013; Le Normand et al., 2014; Song, Pranovich & Holmbom, 2013). For example, Cheng et al. (2013) compared hot-water, ultrasonic assisted, enzyme, and microwave-assisted extractions to isolate bioactive polysaccharides and discovered that the yielded four polysaccharides had similar physicochemical properties, however, the antioxidant activity of the polysaccharides obtained by hot-water extraction was stronger than those isolated with other methods. Hot-water extraction combined with some novel assistant methods, such as microwave, ultrasonic, and enzymatic pretreatment, increases the extraction efficiency and yield of products. For example, enzymatic pretreatment of the raw material before extraction normally results in a reduction in extraction time, lowers energy consumption, minimizes the usage of solvents, increases the yield, and maximally preserves biological activities of the product when compared to non-enzymatic methods (Chen et al., 2014; Dong, Wang, & Wang, 2011; Jia et al., 2013; Lazaridou, Chornick, Biliaderis, & Izydorczyk, 2008; Puri, Sharma, & Barrow, 2012). Recently, ionic liquids have also been developed to extract polysaccharides at low temperature and short time (Abe, Fukaya, & Ohno, 2010).

Further purification of bioactive polysaccharides from crude extracts is of high importance, which ensures understanding of the relationship between structures and the safety of the future biomedical, pharmaceutical, and food applications. This can be done with a combination of several techniques, such as ethanol precipitation, fractional precipitation, ion-exchange chromatography, gel filtration, and affinity chromatography by taking advantages of particular properties of the desired compound such as acidity, polarity, and molecular size (Jin et al., 2013).

4. Functionalization of polysaccharides

The naturally bioactive polysaccharides from different sources could offer numerous bioactive properties and benefit humanity in health care, as reviewed above. It is known that the structural features of the polysaccharides, such as degree and steric configuration of substitutions, linkages of monosaccharides and substitutes, and molar mass and its distribution play a critical role on their physicochemical (e.g. solubility and fluid capability) and bioactive properties (Ngo & Kim, 2013). Therefore, the modification of natively bioactive polysaccharides to extend their applications in both traditional and newly explored biomedical areas, such as tissue engineering, controlled drug delivery and release, and wound healing/dressing, is of high importance. Besides, the functionalization of those polysaccharides that do not possess innate bioactivity to introduce bioactivity by designing cost-effective approaches is also attracting increasing attention. This section will focus on the functionalization of polysaccharides, mainly including plant derived polysaccharides, i.e. cellulose and hemicelluloses, and starch as summarized in Table 2. Other non-plant derived polysaccharides such as chitin and chitosan, alginate,

Table 2 – Summary of polysaccharide modification and applications of the functionalized derivatives.

Polysaccharides	Modification approaches	Description of reactions or products	Potential applications	Ref.
Cellulose	Etherification	Methyl-/carboxymethyl-/ethyl-/hydroxyethyl-/hydroxypropyl-/hydroxypropylmethyl-/cyanoethyl-cellulose	Pharmacy	Kalia, Kaith, and Inderjeet (2011) , Li and Mei (2006)
	Selective oxidation	TEMPO mediated oxidation, periodate oxidized 2,3-dialdehyde cellulose	Drug delivery system, wound healing, regulation of postprandial glucose and insulin level	Lacin (2014) , Shimotoyodome et al. (2011) , Valo et al. (2013) , Zhu et al. (2001)
	Graft copolymerization	Chemical redox initiation or irradiation methods to introduce different monomers, e.g. acrylic acid, acrylamide, acrylonitrile, methyl methacrylate, ethyl acrylate etc.	Stimuli-responsive drug delivery	Mohd Amin et al. (2013) , Thakur, Thakur, and Gupta, (2013b)
Chitin/chitosan	Etherification	O-carboxymethyl and N-carboxymethyl derivatives obtained when the carboxymethylation takes place at carboxyl groups and free amino groups respectively.	Target drug delivery, hemostatic dressings	Zhang et al. (2010)
	Quaternization (etherification)	Trimethyl chitosan chloride, N-propyl-N,N-dimethyl chitosan, N-furfuryl-N,N-dimethyl chitosan, N-diethylmethylamino chitosan. Different degree of quaternization (methylation) of amino groups in chitosan can be achieved with methyl iodide in alkaline solution of N-methyl pyrrolidinone	Absorption enhancer for test drugs, gene carriers, controlled drug releaser, antibacterial agents	Mourya and Inamdar (2008)
	Graft copolymerization	Initiated by free radicals initiator systems, irradiation methods, or grafting via enzymatic methods (e.g. tyrosinase)	Wound-dressing materials, drug delivery, tissue engineering, antimicrobial agents	Alves and Mano (2008) , Ito et al. (2013)
Alginate	Esterification	Propylene glycol alginate, synthesized by reaction with propyleneoxide. Dodecyl alginate, prepared by reaction of tetrabutylammonium salts of alginic acid with dodecyl bromide	Amorphous solid dispersion of drugs	d'Ayala et al. (2008) ; Pawar and Edgar (2013)
	Oxidation	Selectively breaks the vicinal glycols and introduces new reactive groups, i.e. two aldehyde groups	Tissue engineering	Bouhadir et al. (2001) , Kim et al. (2012)
	Graft copolymerization	Chemical redox initiation, microwave initiated synthesis, or microwave assisted synthesis to introduce different monomers (vinyl or acrylic compounds, e.g. poly(N-isopropylacrylamide))	Temperature and pH responsive hydrogel for delivery of proteins or drugs, wound healing dressing	Gao, Liu, Chen, Jin, and Chen (2009) , Isiklan and Kucukbalci (2012) , Pawar and Edgar (2012) , Wong (2011) , Xu et al. (2013)
	Layer-by-layer self-assembly	Repeated deposition of oppositely charged polymers (e.g. negative charged alginate and positive charged chitosan in acid conditions) on material surfaces as polyelectrolyte multilayers	Cell adhesion and spreading, drug and DNA delivery	Caridade et al. (2013) , Hu and Tsou (2014) , Liu, Liu, Liu, Li, and Liu (2013) , Silva et al. (2013a)
Starch	Esterification			Tupa et al. (2013)

Table 2 (continued)

Polysaccharides	Modification approaches	Description of reactions or products	Potential applications	Ref.
Hyaluronic acid (HA)	Etherification	Prepared by reaction of starch with fatty acid chlorides/vinyl esters/anhydride/carboxylic acids as reactants. E.g. Starch acetates, starch butyrates	Used as superdisintegrant and matrix former in capsules and tablet formulations, controlled release, maintaining human colonic function	BeMiller and Whistler (2009), Tharanathan (2005)
	Esterification	Methyl/hydroxypropylmethyl/hydroxyethylmethyl starch Esterification of HA by alkylation using alkyl halides (chlorides, iodides, bromide), by using diazomethane, and by using epoxides	Pharmaceutical application Cell carrier for skin wounds, drug carrier	
	Amidation	Amidation of HA in water or of HA's TBA salt in organic solvent with coupling agents, e.g. EDC, NHS	HA–drug conjugates for controlling release, target specific delivery of biomolecules	Oh et al. (2010) Bulpitt and Aeschlimann (1999), Kong, Oh, Chae, Lee & Hahn (2010) Crescenzi et al. (2003), Maleki, Kjoniksen, and Nystrom (2007)
	Ugi condensation	Formation of diamide linkage between polysaccharides chains by using formaldehyde, cyclohexyl isocyanide and diamine	Controlled drug delivery	
Xylans	Graft-copolymerization	Free radical graft copolymerization of xylan-rich hemicelluloses with acrylic acid yielded ionic xylan-rich hydrogels	Adsorption, separation, and drug release applications.	Peng et al. (2011)
(Galacto) glucomannans	Amidation & Enzymatic modification	Conjugating of tyramine with spruce arabinoglucuronoxylan by EDAC/NHS first then cross-linking using horseradish peroxidase and H ₂ O ₂	Cell culture, tissue engineering.	Kuzmenko et al.
	Hydrolysis	Partial hydrolysis of Konjac glucomannan by acid or enzymes	Food ingredient and prebiotic	Al-Ghazzewi et al. (2007)
	Esterification	Methacrylated galactoglucomannan cross-linked hydrogel	Drug delivery	Edgar, Heinze, and Buchanan, (2009)
	Oxidation	TEMPO-mediated oxidation	Further functionalization platform, e.g. functional biocomposites	Leppänen et al. (2013)
Xyloglucan	Enzymatic modification	Selectively oxidize the primary hydroxyl groups of galactosyl to aldehyde functionalities using galactose oxidase	Potential platforms for further functionalizations, e.g. development of new anticoagulant and antithrombotic drugs	(Gatenholm and Tenkanen (2004), Leppänen et al. (2014), Parikka et al. (2012), Parikka et al. (2009), Xu et al. (2012)
	Chemo-enzymatic modification	Incorporation of different chemically reactive groups or functional moieties, such as biotin into the xyloglucan by xyloglucan endotransglycosylase. Regioselectively oxidize the primary alcohols of galactosyl to aldehydes using galactose oxidase	Potential platforms for further functionalizations, e.g. functional biocomposites, in vitro diagnostics, biomolecular capture or detection	(Brumer et al. (2004), Xu et al. (2012)
Pectins	Graft copolymerization	Grafting with poly(N-vinylpyrrolidone) to prepare hydrogel copolymer	Colon-targeted drug delivery	Fares, Assaf, and Abul-Haija (2010)
	Cross-linking	Cross-linking via calcium or prepare composites with other polymers such as ethylcellulose and hydroxypropylmethyl cellulose	Controlled drug delivery	Liu et al. (2003)

and hyaluronic acid are also subjected to review. The aims of modification or functionalization include, but are not limited to, the improvement and/or introduction of bioactivity, biocompatibility, control of biodegradability, as well as manufacturing and shaping for biomedical, pharmaceutical, and food applications (Cumpstey, 2013; d'Ayala, Malinconico, & Laurienzo, 2008). When considering the application of the modified or functionalized polysaccharides, safe and green approaches such as enzymatic methods are preferred because of their selectivity and non-toxic solvent medium.

4.1. Cellulose

Cellulose is the most abundant polysaccharide in nature. Its value has been recognized in numerous traditional industries, such as construction, pulp and papermaking, and textile industries. For upgrading the value of cellulose, various value-added cellulose derivatives after chemical transformation or functionalization have been developed and utilized in other industries such as food, cosmetic, (bio)medical, and pharmaceutical. However, the application of cellulosic material is limited due to the difficulty in processing, for example, the high crystallinity degree and rigid intra/intermolecular hydrogen bonds which result in its insolubility in most solvents (Tashiro & Kobayashi, 1991).

Generally, the hydroxyl group is the most targeted reactive group on the cellulose chain. Chemical functionalizations of cellulose based on hydroxyl group include esterification, etherification, selective oxidation, graft copolymerization, and intermolecular crosslinking reaction (Pérez & Samain, 2010) as summarized in Table 2. However, the primary and secondary hydroxyl groups show different reactivity in different conditions. For example, the reactivity order of these hydroxyl groups during etherification reactions in alkaline condition is $C_2\text{-OH} > C_6\text{-OH} > C_3\text{-OH}$, while the reactive order of cellulose acetylation in LiCl/acetic acid dimethylamide (DMAc) shows as $C_6\text{-OH} > C_3\text{-OH} > C_2\text{-OH}$, but when the reaction takes place in LiCl/1,3-dimethyl-2-imidazolidinone, the corresponding order is $C_6\text{-OH} > C_2\text{-OH} > C_3\text{-OH}$ (Heinze, 2005). In addition to the inherent reactivity difference of hydroxyl groups, regioselective control of the substitution of desired hydroxyls with functional groups can be achieved via various protecting and activating approaches as shown in Fig. 1. The difference in accessibility, reactivity, and regioselective control of hydroxyl groups provides the possibility to prepare cellulose derivatives with specific molecular structures for various applications.

Oxidation of cellulose is one of the most important modification methods to prepare value-added cellulose derivatives for further applications. For example, oxidized cellulose and regenerated cellulose are widely used as excellent hemostatic materials in various surgical operations and postsurgical adhesion prevention layers (Wu, He, Huang, Wang, & Tang, 2012). Selective oxidation of cellulose by converting the primary alcohol groups into carboxyl groups is of significance and has been studied intensively, especially for the preparation of nanofibrillated cellulose in recent years (Isogai, Saito, & Fukuzumi, 2011). Selective oxidation of cellulose primary hydroxyl groups into carboxyl and/or aldehyde groups can be achieved through two oxidation systems

(Fig. 1): (1) 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and its derivatives; (2) *N*-hydroxyphthalimide (NHPI), *N*-hydroxybenzotriazole (HBT), and violuric acid (VA). (Biliuta et al., 2013; Coseri et al., 2009). Lately, oral administration of TEMPO-oxidized cellulose with glucose and glyceryl trioleate to mice was found to exhibit characteristic biological activities in reducing postprandial blood glucose, plasma insulin, glucose-dependent insulinotropic polypeptide, and triglyceride concentrations. This finding may suggest potential applications of TEMPO-oxidized cellulose in biomedical fields for human health (Shimotoyodome, Suzuki, Kumamoto, Hase, & Isogai, 2011). The carboxyl groups introduced by these approaches can be utilized for further functionalization. For example, by grafting amine-terminated polyethylene glycol chains (PEG) onto carboxylic sites of the TEMPO-oxidized cellulose, a better steric stabilization and salt tolerance property can be achieved (Araki, Wada, & Kuga, 2000). Besides, topological modification of films prepared from oxidized cellulose via 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)/*N*-hydroxysuccinimide (NHS) chemical activation to produce non-porous, water-resistant substrates for immunoassays and diagnostics application, or to introduce linking biomolecular onto cellulose for immobilizing antibodies and other functionalities for medical and biological application have also been studied recently (Fig. 1) (Arola, Tammelin, Setälä, Tullila, & Linder, 2012; Orelma et al., 2012a; Orelma, Johansson, Filpponen, Rojas, & Laine, 2012b). Ascribed to the gelling properties, biodegradability, biocompatibility, and bioactivity of TEMPO oxidized NFC, its structured hydrogel and aerogel materials have been used for biomedical applications such as scaffold for wound-healing and 3-D cell culture, and drug carrier and controlled release, cosmetic applications such as thickeners and water-retaining agents, and other applications (Bhattacharya et al., 2012; Dong, Snyder, Tran, & Leadore, 2013; Sehaqui, Zhou, & Berglund, 2011; Shimotoyodome et al., 2011; Valo et al., 2013).

Another selective oxidation approach is the periodate oxidation (Fig. 1), which selectively oxidizes the adjacent hydroxyl groups ($C_2\text{-OH}$ and $C_3\text{-OH}$) of cellulose yielding a sugar ring opened product with two aldehyde groups in the C_2 and C_3 position of the glucopyranose units (Calvini, Gorassini, Luciano, & Franceschi, 2006). This opens up untapped possibilities for further functionalization and application. For example, sulfonation of the periodate oxidized 2,3-dialdehyde cellulose with sodium bisulfite yields the corresponding $C_{2/3}$ sulfonates possessing stronger water retention ability (Zhang, Jiang, Dang, Elder, & Ragauskas, 2008).

Other oxidant systems, such as $\text{N}_2\text{O}_4/\text{CCl}_4$, NO_2/CCl_4 , and $\text{HNO}_3/\text{H}_3\text{PO}_4\text{-NaNO}_2$ have also been developed to selectively oxidize cellulose (Fig. 1) (Coseri et al., 2009; Kumar & Yang, 2002; Wu et al., 2012). Oxidized cellulose has shown anti-tumor, immunostimulant, wound healing, and adhesion-prevention properties (Novotna et al., 2013; Zimnitsky, Yurkshtovich, & Bychkovsky, 2004). For example, the calcium/sodium salts of oxidized cellulose prepared from nitrogen oxides in nitric acid have shown immunomodulatory effects in both *in vitro* and *in vivo* tests (Jelinkova, Briestensky, Santar & Rihova, 2002). The carboxyl groups of the $\text{HNO}_3/\text{H}_3\text{PO}_4\text{-NaNO}_2$ oxidized cellulose open up possibilities for immobilization of drugs, the products of which have found

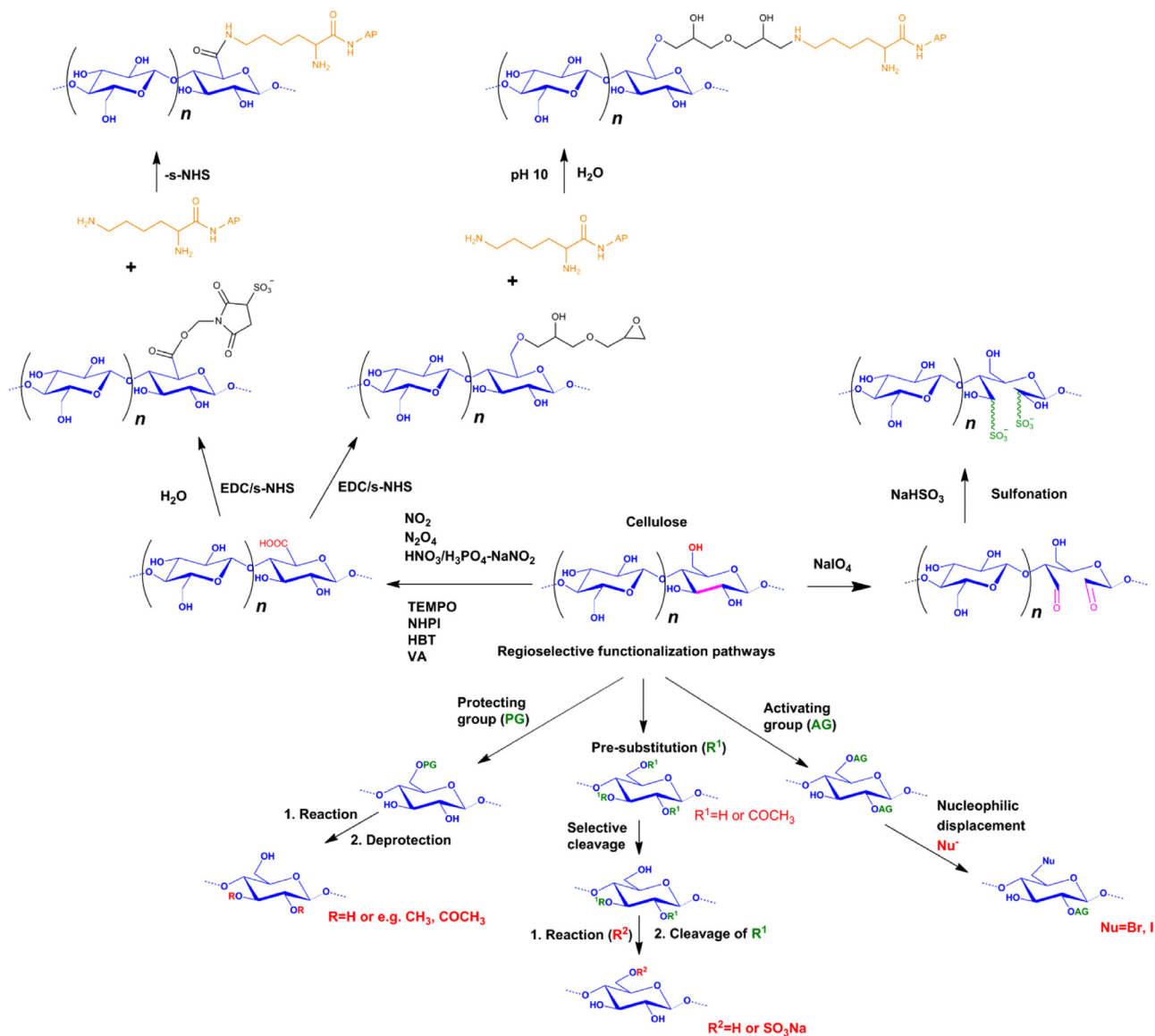


Fig. 1 – Selected pathways for regioselective functionalization of cellulose (adapted from Arola et al., 2012; Biliuta et al., 2013; Coseri et al., 2009; Koschella, Fenn, Ily, & Heinze, 2006; Wu et al., 2012; Zhang et al., 2008).

potential applications as biodegradable macromolecules used in drug delivery systems (Zhu, Kumar, & Banker, 2001).

Graft copolymerization is another approach for cellulose modification via chemical redox initiation methods (ceric ammonium nitrate or ferrous ammonium sulfate–potassium persulfate) or irradiation methods (UV, microwave, and γ -rays). Intensive studies have been carried out on the graft copolymerization of cellulosic polymers with suitable hydrophobic monomers to introduce desired functionalities into the cellulosic backbone, so as to overcome the sensitivity of cellulosic fibers towards water/moisture absorption and poor chemical resistance and thus to improve the existing physicochemical properties of the cellulosic polymers (Bashar, Khan, & Idriss Ali, 1995; Kaur, Kumar, & Sharma, 2010; Rattan, Maitra, Misra, & Kaur, 2008; Thakur, Thakur, & Gupta, 2013a). A biocide cellulose carbamate with antimicrobial properties was prepared by impregnating the fibers in aqueous thiourea solution and subsequently grafting with

acrylonitrile (Dahou, Ghemati, Oudia, & Aliouche, 2010). Stimuli-responsive bacterial cellulose-*g*-poly(acrylic acid-co-acrylamide) hydrogels as drug delivery carriers have been synthesized by graft copolymerization of the monomers onto bacterial cellulose fibers using microwave irradiation. The grafted cellulose hydrogels demonstrated a pH-responsive swelling behavior (reaching maximum swelling at pH 7), suggesting a suitable controlled release in the lower gastrointestinal tract (Mohd Amin, Ahmad, Pandey, & Jue Xin, 2013).

4.2. Hemicelluloses

Hemicelluloses are a type of heterogeneous polysaccharides and are widely distributed in biomass. Hemicelluloses mainly include xylans, glucomannans, arabinans, galactans, and glucans. The diversity of hemicelluloses originates from: (a) sugar constituents, which mainly include glucose, xylose, mannose, galactose, arabinose, fucose, (4-*O*-methyl)glucuronic acid, and

galacturonic acid; (b) glycosidic linkages position and conformation between monosaccharides, e.g., arabinofuranosyl, 1→2,3,4,5,6 linkages; and (c) side group/chain types, distribution, and linkages. Such structural and compositional complexities result in previously unperceived applications. However, as a group of important biopolymers, hemicelluloses have found a broad spectrum of applications both in native and in their modified forms. Generally similar to other polysaccharides, chemical modifications of hemicelluloses mainly include partial hydrolysis, graft polymerization, (regioselective) oxidation, reduction, etherification, esterification, and cross-linking. The modifications bring in new functionality and therefore create novel opportunities to exploit them for various applications such as in food, cosmetic, biomedical, and pharmaceuticals.

4.2.1. Xylans

Xylans are a diverse group of polysaccharides with the common feature of a backbone of β -(1→4)-linked xylopyranosyl units. Substitution or side groups/chains are varying according to different sources and methods of isolation. For example, O-acetyl-4-O-methylglucuronoxylans with (1→2) linked 4-O-methyl- α -D-glucuronic acid side groups and O-acetyl group at C₂ or C₃ are the major hemicelluloses in hardwoods and account for 15–30% of the dry wood. Xylans in softwood account only for 5–10% of the dry wood, and mainly exist as arabino-4-O-methylglucuronoxylans, which have 1→3) linked α -L-arabinofuranose and (1→2) linked 4-O-methyl- α -D-glucuronic acid side groups (Teleman, Tenkanen, Jacobs, & Dahlman, 2002; Viikari, Poutanen, Tenkanen, & Tolan, 2002).

Recently, xylans have gained increasing attention as basis for new functional biopolymeric materials by chemical modifications. Various functional groups can be introduced to xylans by esterification, etherification, and cross-linking for different applications, such as drug delivery, wound dressing, and antimicrobial agents. (Ebringerová & Heinze, 2000; Petzold-Welcke, Schwikal, Daus, & Heinze, 2014; Pohjanlehto, Setälä, Kammiovirta, & Harlin, 2011). For example, introduction of antioxidant activity to xylans for biomedical applications could be achieved by esterification with ferulic acid and sinapic acid (Wrigstedt et al., 2010). Pentosan polysulfate, an FDA-approved oral medicine, was prepared by sulfation of beechwood xylan. It has been known for its anticoagulant properties, anti-inflammatory and anticancer effects, and for lowering cholesterol and triglyceride levels (Doctor & Sauls, 1983; Schuchman et al., 2013). Product derived from xylan and chitosan via the Maillard reaction was found to exert antioxidant and antimicrobial activity (Wu et al., 2014). Peng, Ren, Zhong, Peng, and Sun (2011) reported ionic xylan-rich hydrogels with rapid and multiple responses to pH, ions, and organic solvents, which may allow the use in drug release systems. An *in situ* forming spruce xylan-based hydrogel was synthesized chemo-enzymatically for stem cell culture application (Kuzmenko, Hägg, Toriz, & Gatenholm). This xylan-based hydrogel showed mechanical integrity, interconnected porous structure, high degree of swelling, and supporting the differentiation of mesenchymal stem cells inside the gel, which is worthwhile for further evaluation for tissue engineering purposes. Other typical modifications to prepare xylan derivatives, such as cationic, ionic, and non-ionic xylan derivatives have been previously reviewed (Heinze, Koschella, & Ebringerová, 2003; Petzold-Welcke et al., 2014).

4.2.2. Galactomannans, glucomannans, and galactoglucomannans

The galactomannans and glucomannans belong to the mannan-type polysaccharides, but with different structures. Typical seed (carob, guar, locust bean, tara, etc.) galactomannans contain a β -(1→4)-linked D-mannan backbone to which is attached single α -D-galactose at the C₆ position of D-mannose (Srivastava & Kapoor, 2005). The glucomannans consist of random distribution of β -(1→4)-linked D-glucose and β -(1→4)-linked D-mannose in the main chain. In softwoods, there are additionally side chains of α -D-galactose linked to the mannan backbone, i.e. galactoglucomannans (GGMs). GGMs from wood, such as spruce, are partially substituted with O-acetyl groups at hydroxyl groups of C₂ and C₃, yielding O-acetyl-galactoglucomannans (Willför et al., 2003).

Chemical modifications of galactomannans by esterification, etherification, oxidation, and hydroxypropylation could lead to derivatives such as carboxymethyl, hydroxypropyl, and carboxymethylhydroxypropyl galactomannans (Kamerling & Boons, 2007). Cationic, anionic, and nonionic GGM have been synthesized and reported in our group as summarized in Fig. 2.

GGM from wood, e.g. spruce, represents the main hemicellulose component of softwoods and as such have been reported to show immunomodulating and radical-scavenging activities in native as potential additives with immune-potentiating and antioxidant properties in food products and pharmaceutical formulations (Ebringerová et al., 2008; Laine et al., 2010). Chemical modifications of GGM from forestry sources have also been extensively studied (Kisonen et al., 2012, 2014; Leppänen et al., 2013). For example, methacrylation reaction has been taken to prepare cross-linked GGM hydrogel for drug delivery (Lindblad, Dahlman, Sjöberg, & Albertsson, 2009). Sulfation and carboxymethylation of GGM have been studied by Doliška et al. (2012) to increase their antithrombotic properties, and the synergistic effect of carboxymethylation and sulfation was found to play the most important role in the antithrombotic effect.

Enzymatic modification with different enzymes provides alternative environmentally friendly and specific approaches (Tenkanen, 2003). Regioselective oxidation of galactose-containing polysaccharides, e.g. GGM from spruce and guar gum (galactomannan) from the seed of leguminous shrub *Cyamopsis tetragonoloba*, can be achieved by using galactose oxidase which selectively oxidizes the primary hydroxyl groups of the galactosyl to aldehyde functionalities (Fig. 2). The oxidized galactose-containing polysaccharides can be further tailored at the selectively introduced aldehyde groups towards further functionalizations, e.g. development of new anticoagulant and antithrombotic drugs applications (Hartmans et al., 2003; Leppänen et al., 2014; Parikka et al., 2012; Xu, Spadiut, Araújo, Nakhai, & Brumer, 2012).

Partially acidic or enzymatic hydrolysis have been applied to degrade native konjac glucomannan for food ingredient and prebiotic applications, the resultant konjac glucomannan with low molecular mass has been reported to show some attractive biological activities, such as cholesterol lowering, bulking for weight reduction, and to reduce the risk of constipation (Al-Ghazzewi, Khanna, Tester, & Piggott, 2007).

4.2.3. Xyloglucans

Xyloglucans are the major hemicelluloses in the primary cell walls of higher plants, they have a common structure of

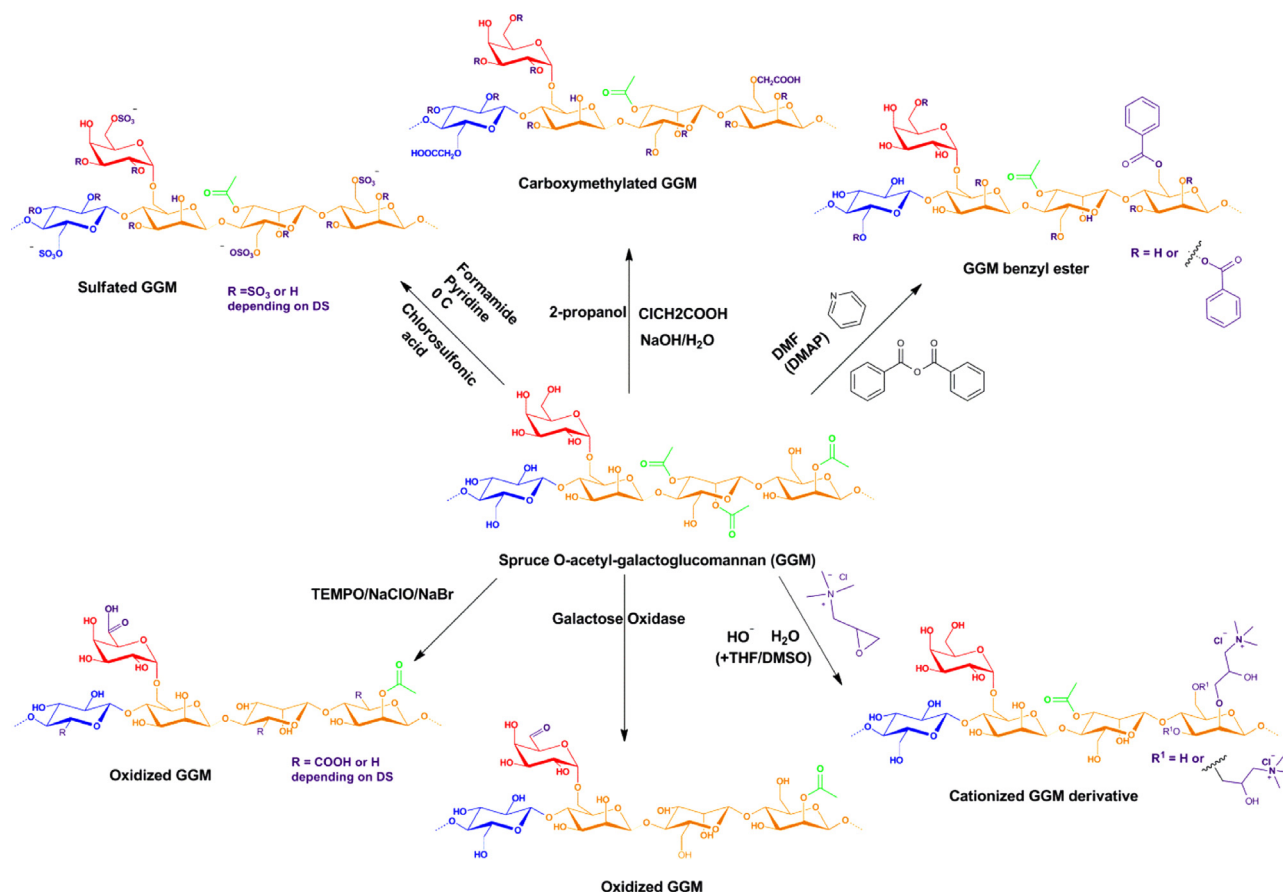


Fig. 2 – Chemical modifications of spruce galactoglucomannan to prepare anionic/cationic/nonionic derivatives (adapted from Doliška et al., 2012; Kisonen et al., 2012, 2014; Leppänen et al., 2013, 2014; Xu et al., 2011).

β -(1→4)-linked D-glucan, and three out of four glucose residues are substituted with α -D-(1→6) xylose. Depending on the source of the xyloglucans, further substituted residues of xylose is β -(1→2)-linked D-galactose, which in turn is sometimes substituted with α -fucosyl residues (Gidley et al., 1991; Kochumalayil, Zhou, Kasai, & Berglund, 2013).

Xyloglucans provide stronger bioavailability of drug and longer residence times, and therefore, has been used as skin patches, oral or rectal drug delivery, and for intraperitoneal injections (Coviello, Matricardi, & Alhaique, 2006). Chemical or chemo-enzymatic modifications to prepare various xyloglucan derivatives can be performed for medical and other applications. For example, sulfated xyloglucan and its selenium ester have been reported to show antioxidant activity and antitumor activity (Cao & Ikeda, 2009).

Chemo-enzymatic modifications of xyloglucan have also been intensively studied. Xyloglucan endotransglycosylase (XET), which transfers glycosyl moieties to carbohydrate acceptors, readily accepts not only xyloglucan polymers, but also xyloglucan oligosaccharides, even after chemical modifications. Thereby, various functional moieties, such as biotin, aminoalcohol and its derivatives, can be introduced to xyloglucan. By taking advantage of the high affinity between xyloglucan and cellulose, the functionalized xyloglucan can be bound to different cellulosic surfaces to prepare functional materials as shown in Fig. 3 (Brumer, Zhou, Baumann, Carlsson, & Teeri, 2004).

Another important chemo-enzymatic approach is to regioselectively oxidize the primary hydroxyl groups of galactose on the side chains of xyloglucan to aldehydes by using galactose oxidase (Parikka et al., 2009). Judicious choices of the functional group allow further *in situ* surface modification. For example, Xu et al. (2012) attached propargylamino groups to yield multialkynylated conjugates, which are clickable by “click chemistry” for desired applications, such as *in vitro* diagnostics, (bio) molecular capture, and detection as illustrated in Fig. 3.

4.3. Pectins

Pectins are heterogeneous polysaccharides with three main domains: α -(1→4)-linked linear homo-galacturonic backbone (HG) alternating with two types of highly branched rhamnogalacturonans regions designated as RG-I and RG-II. RG-I is substituted with side chains of arabinose and galactose units. RG-II has a highly conserved structure, consisting of a HG backbone branched with eleven different monosaccharides, including some rare sugars such as 2-O-methylxylose, 2-O-methylfucose, apiose, aceric acid, 2-keto-3-deoxy-D-manno-octulosonic acid, and 3-deoxy-D-lyxo-2-heptulosaric acid (Le Normand et al., 2014; Ridley, O'Neill, & Mohnen, 2001). In all natural pectins, some of the carboxyl groups exist in the methyl ester form.

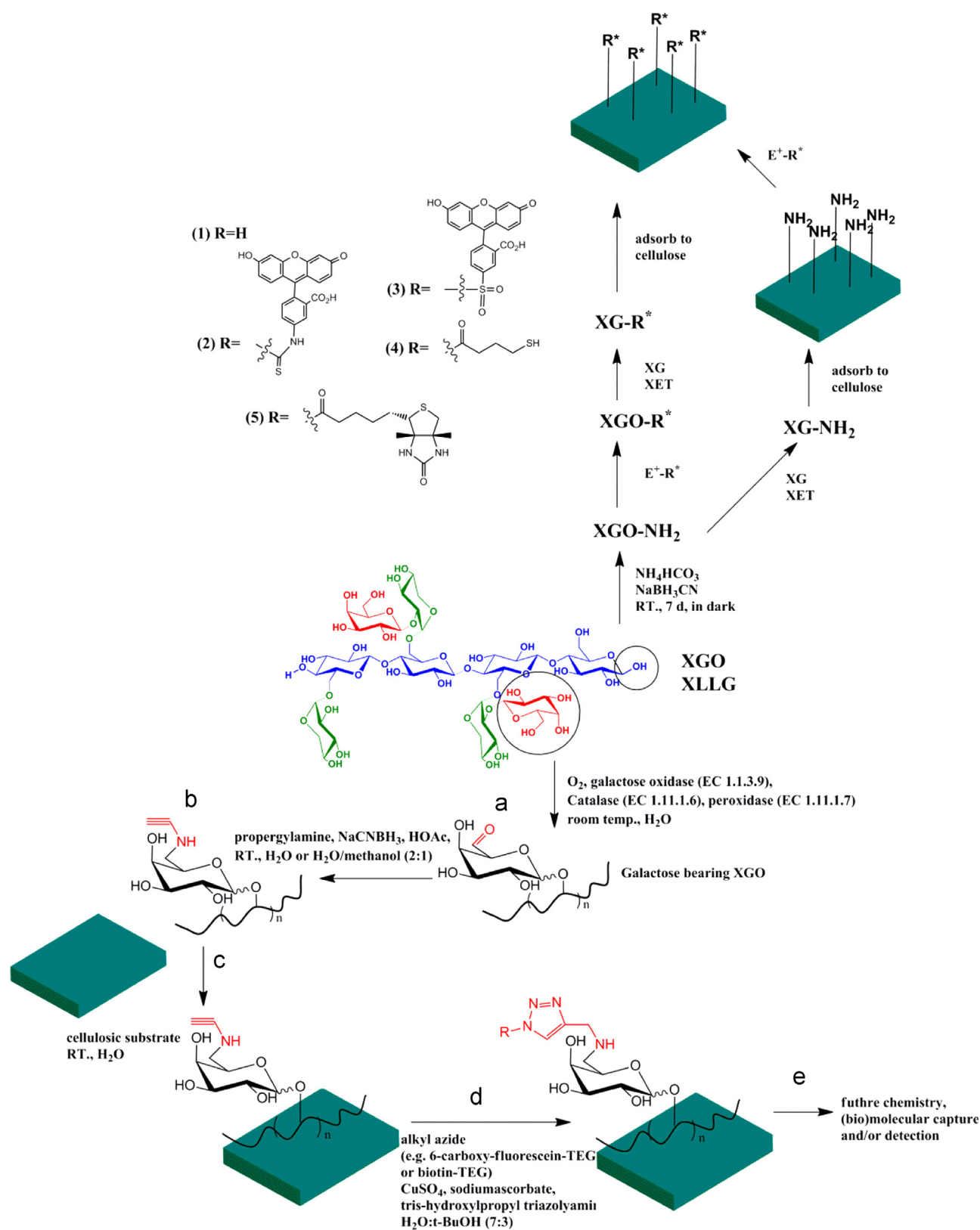


Fig. 3 – Chemo-enzymatic modifications of xyloglucan via XET techniques and regioselectively oxidation plus click chemistry. (pathway up) adapted with permission from (Brumer et al., 2004). Copyright (2004) American Chemical Society. (pathway below) adapted with permission from (Xu et al., 2012). Copyright (2012) Wiley.

Pectins, mainly from citrus peel and apple pomace, are widely used in the food industry as gelling or thickening agents and in the pharmaceutical industry as an excipient due to its non-toxicity, low production costs, and gelling activity properties. Because pectin is intact in the upper gastrointestinal tract and degraded by colonic microflora, pectin-derived drug carriers provide promising potential for colon-specific drug delivery. Gelation of pectin, calcium cross-linked pectinate, composites of pectin and other polymers such as ethylcellulose and hydroxypropylmethylcellulose have been examined and tested for controlled drug delivery (Liu, Fishman, Kost, & Hicks, 2003). Modification of pectin via grafting with poly(*N*-vinylpyrrolidone) (PVP) has also been reported to form an effective hydrogel that can make effective colon-targeted drug delivery (Fares, Assaf, & Abul-Haija, 2010). In addition to food and pharmaceutical applications, a recent study reported that pectins (rhamnogalacturonan RG-I domain ramified with highly-branched arabinans) extracted from spruce bark showed immunomodulating activities, which suggested a potential application as immunostimulant (Le Normand et al., 2014). The hydrogel of pectin has been explored in tissue engineering applications for bone cells culture and promoting the nucleation of minerals, and in wound healing applications for binding active drugs or growth factors and protecting against bacterials (Munarin, Tanzi, & Petrini, 2012).

4.4. Starch

Starch is a biopolymer synthesized in a granular form by green plants and consists of two major components, i.e. linear amylose with α -(1 \rightarrow 4)-D-glucopyranose, and branched amylopectin with α -(1 \rightarrow 4)-D-glucopyranose backbone and 5–6% of α -(1 \rightarrow 6)-branch linkages (Pérez & Bertoft, 2010). Minor constituents such as lipids, proteins, and minerals are present in starch and the levels vary with the origin (Waterschoot, Gomand, Fierens, & Delcour, 2014). Starch is an excellent material for industrial uses due to its non-toxic, renewable and biodegradable properties. However, the intrinsic properties such as thermal, mechanical, and biological properties and poor processability of starch have limited its direct applications (Khan & Ahmad, 2013). Thus, various chemical, physical, and enzymatic modifications or blending with other materials have provided solutions to achieve more desirable properties.

Similar to the cellulose, conventional chemical modifications of starch based on the primary and secondary hydroxyl groups include esterification, etherification, oxidation, and graft copolymerization (Table 2).

Starch esters are generally prepared by reacting with fatty acid chlorides, fatty acid vinyl esters, carboxylic acids, and fatty acid methyl ester in organic solvents such as pyridine, toluene, DMSO, and DMAc/LiCl (Grote & Heinze, 2005; Xie & Wang, 2011). Starch esters have been developed for pharmaceutical applications, e.g. used as superdisintegrant and matrix former in capsules and tablet formulations; and for medical application to maintaining human colonic function and preventing colonic disease (Tupa, Maldonado, Vazquez, & Foresti, 2013).

Quaternary ammonium cationic starches, the major commercial starch ethers, are commonly prepared by the reaction of an aqueous alkaline solution of 2,3-epoxypropyltrimethyl ammonium chloride or 3-chloro-2-hydroxypropyltrimethyl ammonium chloride (Pigorsch, 2009). The quaternary ammonium-substituted cationic starches may form nanoparticles with anionic sodium tripolyphosphate. The nanoparticles could entrap hydrophobic molecules, providing a great potential as nanosized carrier in health care and environmental sciences (Rutkaite, Bendoraitiene, Klimaviciute, & Zemaitaitis, 2012).

Hydroxyethyl starch is semisynthetic starch ether by reacting with ethylene oxide in alkaline medium, and it has been used as a plasma volume expander and cryoprotectant in medicine. Further functionalization by esterification with lauric, palmitic, and stearic acid using dicyclohexyl carbodiimide and dimethylaminopyridine has been used to prepare a fully biodegradable amphiphilic polymer for drug carrier application (Besheer, Hause, Kressler, & Mader, 2007). Lately, a nanocarrier based on hydroxyethyl starch for active receptor-mediated targeting was synthesized (Baier et al., 2012). The hydroxyethyl starch folic acid conjugate nanocarriers could be of high interest for the development of receptor mediated targeting using polymeric nanocapsules to deliver and accumulate their encapsulated molecules to the targeted area.

Selective oxidation of starch with N_2O_4 or a TEMPO/NaClO/NaBr system can exclusively yield carboxylates on the primary hydroxyl groups. Such oxidation approaches can also be applied to selectively oxidize starch derivatives, which bear another oxidation candidate primary hydroxyl group (e.g. hydroxyethyl starch) (BeMiller & Whistler, 2009). Dialdehyde starch can be prepared by oxidation of vicinal alcohol groups to aldehyde groups at the C₂ and C₃ by using periodic acid or periodate. The yielded aldehyde groups may react with alcohols, amines, hydrazines, and hydrazides to provide additional functionalized products and applications (Haaksman, Besemer, Jetten, Timmermans, & Slaghek, 2006).

4.5. Chitin and chitosan

Application of chitin/chitosan has been extensively developed, e.g. in oral administration for lowering serum cholesterol concentration and hypertension and in ophthalmic preparations for improving the retention and biodistribution of drugs applied topically onto the eyes (Muzzarelli & Muzzarelli, 2005). However, due to the semi-crystalline structure of chitin with extensive hydrogen bonds, the chitin is insoluble in common solvents, and this has limited the development and processing of chitin for practical applications. The chitosan is normally insoluble in aqueous solution above pH 7, but its free amine groups can be protonated in dilute acids (pH 6) and the chitosan molecule becomes soluble. Such pH-dependent solubility might provide potential applications as sensors. Nevertheless, it also poses challenges, especially for biological applications that require neutralized environment. Therefore, further modification of chitin and chitosan to introduce desired physicochemical and biochemical properties without any changes in their fundamental skeleton is of significance for a breakthrough in utilization of their unique features and activities (Oliveira & Reis, 2011).

The active groups or the possible reaction sites of both chitin and chitosan mainly include the free amino groups, primary and secondary hydroxyl groups, and acetamido groups. As summarized in Fig. 4, chemical reactions targeted at the hydroxyl groups, such as etherification, esterification, cross-linking, graft copolymerization, and O-acetylation, can be used for modification. Chemical reactions targeting the amino groups of chitin and chitosan include acetylation, quaternization, Schiff base reaction (reactions with aldehydes and ketones), and grafting (Jain et al., 2013; Pillai, Paul, & Sharma, 2009). Modification of chitosan with sugars onto the amino groups (Fig. 4, method (A), method (B)) provides a promising approach to introduce desired sugars for various applications in specific drug, DNA, and antibody carriers by incorporation of cell-specific sugars that are specifically recognized by cells, viruses, and bacteria (Kim, 2013; Yao, 2012).

Carboxymethylation can take place at hydroxyl groups of chitin and chitosan to yield O-carboxymethyl derivatives, and can also take place at the free amino groups of chitosan to yield N-carboxymethyl derivatives (Fig. 4). Derivatization of chitosan by introducing alkyl or carboxymethyl groups onto the C₃ and/or C₆ hydroxyl groups to prepare e.g. O-carboxymethyl chitosan can significantly increase the solubility at neutral and even alkaline conditions at the same time maintaining the cationic properties. Such O-carboxymethyl chitosan was used to enhance the biocompatibility of polylactic acid film surfaces, which had higher cell adhesion and proliferation than that of the unmodified one (Alves & Mano, 2008; Cai, Yao, Li, Yang, & Li, 2001). Carboxymethyl chitin, a water-soluble anionic polymer was selectively modified to prepare antitumour drug conjugates (Rinaudo, 2008). A

microsphere of 6-O-carboxymethyl chitin was reported as a potential vehicle for targeted drug delivery to the liver due to its preferentially located and long retainment in the liver and spleen after i.v. injection (Hata, Onishi, & Machida, 2000). An amphiprotic ether derivative that contains both carboxyl groups and amino groups can be prepared when the substitution moieties bear carboxyl groups (Alves & Mano, 2008). Simultaneous incorporation of substituents, for example carboxymethyl groups, onto some of the amino and primary hydroxyl sites of the glucosamine units can also be achieved by using chitosan, sodium hydroxide, isopropanol with chloroacetic acid as solvent (Khan & Ahmad, 2013).

Graft copolymerization is an important approach for modification of the chitin and chitosan towards medical and pharmaceutical applications, such as in orthopedic/periodontal materials, wound-dressing materials, tissue engineering, and controlled drug/gene delivery (Ito, Yoshida, & Murakami, 2013). Graft copolymerization of chitin and chitosan can be initiated by chemical (free radicals) initiator systems, by radiation methods and by enzymatic grafting methods (Alves & Mano, 2008). Graft copolymerization of chitosan with “presynthesized” polymers instead of their monomers can help to control the side-chain molar mass and avoid the absence of residual monomers. For example, Lu, Xu, Zhang, Cheng, and Zhuo (2008), prepared a chitosan-based copolymer, which had a good potential as efficient nonviral gene vectors, through grafting polyethylenimine (800 Da) to N-maleated chitosans. Kumar et al. (2012) utilized polyacrylamide, instead of normal acrylamide monomer, for grafting onto chitosan with high grafting efficiency (GE=92%) and grafting ratio (GR=263%). The resulting macroporous polyacrylamide-grafted-chitosan exhibited superior neuronal

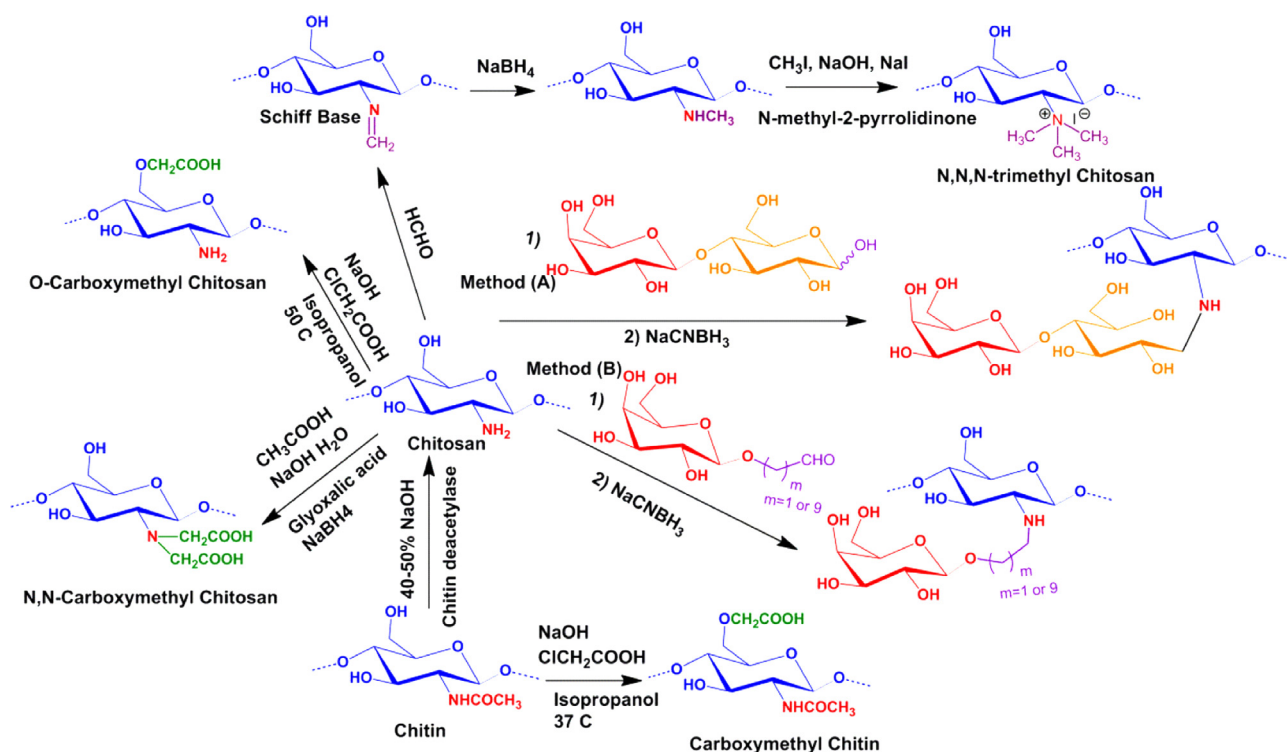


Fig. 4 – Chemical modification of chitin/chitosan (adapted from Kean, Roth, & Thanou, 2005; Khan & Ahmad, 2013; Kim, 2013; Nemtsev, Gamzazade, Rogozhin, Bykova, & Bykov, 2002).

cell infiltration owing to the anisotropic porous architecture, high-molar-mass mediated robustness, and superior hydrophilicity, as well as surface charge due to the acrylic chains and the substrate could act as a potential neural cell carrier applied in scaffolds for neural tissue engineering.

Based on graft copolymerization and a molecular imprinting technique, chitosan has been used to prepare recognition materials, such as metal ions, dyes, and proteins, and therefore, could be used for special absorption of template molecules mimicking natural recognition materials such as antibodies for diagnostics (Kyzas, Lazaridis, & Bikiaris, 2013; Monier & El-Mekabaty, 2013). For example, Dan et al. (2013), prepared a molecular imprinted chitosan gel to recognize the template ovalbumin. Their resulting gels showed notable adsorption capacities and high special selectivity to the template protein. Similarly, Fu, Zhao, Yu, Liu, and He (2007) synthesized a molecularly imprinted polymer (MIP) gel using bovine serum albumin (BSA) as a template and based on copolymerization of acrylamide with *N,N'*-methylenebisacrylamide on chitosan in aqueous medium. The resultant MIP gels were found not only to show significantly higher imprinting efficiency and specificity for BSA, but also much better stability in rebinding of the imprint molecules after adsorption-regeneration cycles.

Blends or composites of chitin or chitosan with synthetic or natural polymers, such as polyethylene glycol, polylactic acid, polypyrrole, collagen, starch, and with inorganic materials such as bioactive glass and ceramics, for drug delivery systems, tissue-engineering, and other medical applications have recently been intensively studied (Jayakumar et al., 2011; Kumar, Muzzarelli, Muzzarelli, Sashiwa, & Domb, 2004; Nakamatsu, Torres, Troncoso, Min-Lin, & Boccaccini, 2006; Rinaudo, 2008). Furthermore, similar to alginate as listed in Table 2, layer-by-layer or multilayer coating techniques have been developed to prepare chitosan-based polyelectrolyte complexes with 2D and 3D structures such as freestanding films, capsules, and porous scaffolds. Hyaluronic acid, alginate, chondroitin sulfate, and hydroxyapatite have also been applied with chitosan to prepare multilayer-structured biomaterials based on the layer-by-layer technique for tissue-engineering applications (Miranda, Silva, Reis, & Mano, 2011; Rinaudo, 2008; Santo, Gomes, Mano, & Reis, 2012; Schneider, Richert, Francius, Voegel, & Picart, 2007; Silva et al., 2013a; Silva et al., 2013b).

4.6. Alginate

Seaweed polysaccharides from the marine plants represent the most abundant polysaccharides in the sea, and alginate is one of the most widely explored seaweed polysaccharides (Wang, Wang, & Guan, 2012). It's a linear block copolymer which composed of β -(1 \rightarrow 4)-linked D-mannuronic acid (M block) and α -L-guluronic acid (G block) units arranged with varying proportion of GG, MG, and GM blocks (Fig. 5) (d'Ayala et al., 2008; Khan & Ahmad, 2013; Rehm, 2009). In the tissue-engineering and cell immobilization fields, the use of alginate for cartilage regeneration is well known due to its gelling and stabilizing properties, in which the G-blocks serve to introduce a steric hindrance and to provide folded and rigid structural conformation (Khan & Ahmad, 2013; Rinaudo,

2008; Spiller, Maher, & Lowman, 2011). However, the drawbacks of inadequate mechanical properties, uncontrollable degradation profiles, and lack of cell recognition signals have limited its medical application. Notably, carboxyl groups and hydroxyl groups along the backbone of the alginate enable various modification approaches to enhance or tailor the properties such as physicochemical, biological, mechanical, and other desired properties (Oliveira & Reis, 2011).

Conventional chemical modification of alginate mainly include graft copolymerization, oxidation, crosslinking with polyvalent cations and/or cationic polymers, sulfation, and esterification targeting the hydroxyl groups and carboxyl groups, and also aldehyde groups after rupture of C₂ and C₃ carbon-carbon bond as reviewed previously (Khan & Ahmad, 2013; Yang, Xie, & He, 2011) and summarized in Fig. 5.

Esterification as a simple method to introduce alkyl groups onto the backbone of the alginate was successfully commercialized decades ago; and the propylene glycol alginate (PGA, Fig. 5) is currently the most representative commercial product (d'Ayala et al., 2008). Esterification of alginate to introduce long alkyl chains can be achieved by reaction with alkyl halides, but the alginate needs to be converted into its tetrabutylammonium salt (TBA) at first. For example, dodecyl alginate was prepared by the reaction of the TBA salt of alginic acid with dodecyl bromide in DMSO (Pawar & Edgar, 2013). However, the partial or total substitution of carboxyl groups after esterification might result in a reduced gelling capacity, which is the most attractive feature of alginate.

The periodate oxidation that selectively cleaves the vicinal glycols (C₂-OH, C₃-OH) and introduces new reactive groups is an alternative approach to modify the alginate while maintaining the gelling properties. Due to the slow degradation rate of alginate, partial periodate oxidation has been reported to accelerate the biodegradation rate of the oxidized alginate and this has found application in tissue engineering (Bouhadir et al., 2001; Rinaudo, 2008). For example, partially periodate oxidized injectable alginate hydrogels have been developed to provide a suitable delivery vehicle for stem cells to engineer adipose tissue (Kim et al., 2012). Actually, such selective oxidation is a classical pre-modification method due to the obtained new reactive groups with larger rotational freedom. Various graft copolymerizations or reductive amination can be further carried out based on such pre-modified intermediate product as shown in Fig. 5 (Yang et al. 2011). For example, low-molar-mass polyethylene glycol (mono-carboxyl terminated), a highly biocompatible polymer, was grafted onto a sodium alginate, which was first modified by inserting a given amount of amine functionalities. The retained gelation characteristics and increased biocompatibility and pore dimension of the alginate-PEG copolymers are requirements for gel entrapment devices and microencapsulation techniques (Laurienzo, Malinconico, Motta, & Vicinanza, 2005). By controlling the degree of alginate oxidation, a crosslinked bio-adhesive alginate-PEG system with controllable mechanical properties, swelling, and degradation rates have been developed (Jeon, Samorezov, & Alsberg, 2014). The oxidized alginate itself is also promising material with improved biodegradability due to the presence of more reactive groups, which

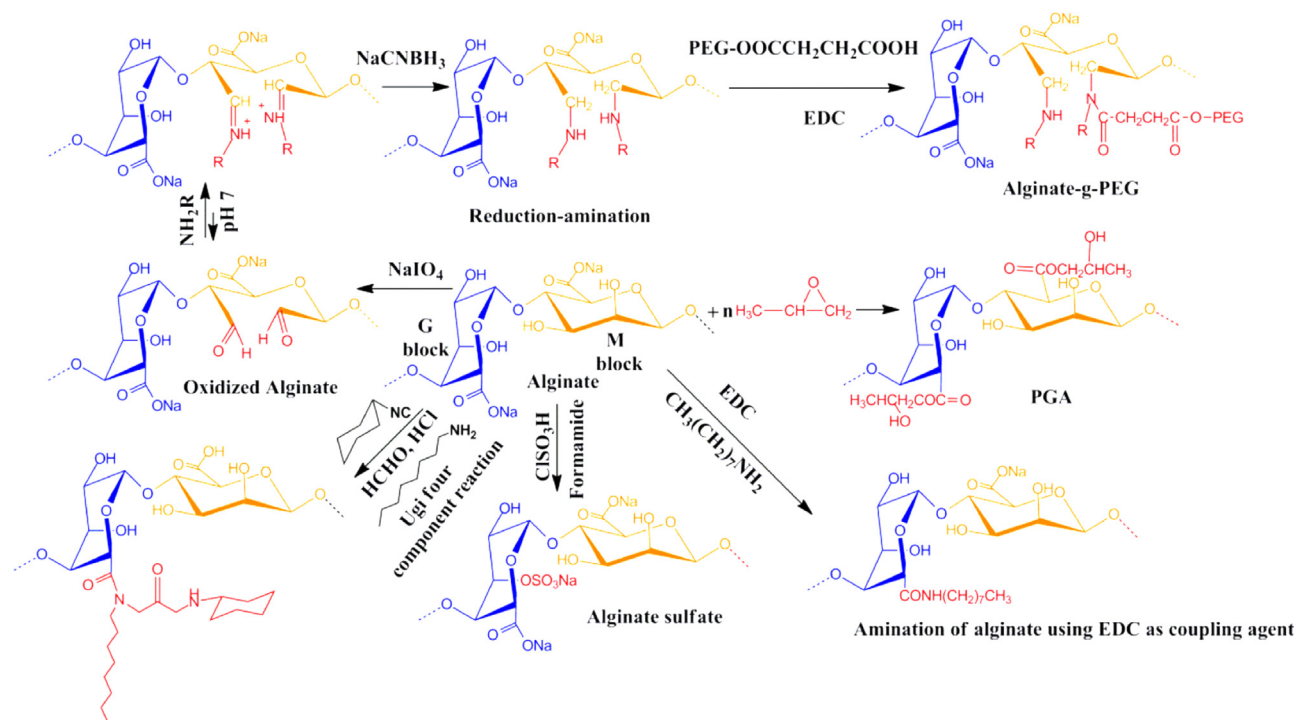


Fig. 5 – Chemical modification of alginate (adapted from d'Ayala et al., 2008; Yang et al., 2011).

contribute to faster degradation when applied in a controlled drug delivery system (Yang et al., 2011).

Ugi reaction has been applied to modify the alginate to form a bis-amine (Fig. 5). Amidation reaction (Fig. 5) has been applied to form amide linkage between amine bearing molecules (e.g. EDC, NHS, 2-chloro-1-methylpyridinium iodide (CMPI), etc.) and the carboxylate moieties on the alginate (Yang et al., 2011).

Grafted alginate copolymers have recently been developed for biomedical applications. An alginate-based pH- and temperature-responsive hydrogel was synthesized by grafting of poly (N-isopropylacrylamide) to the alginate backbone using EDC/ NHS as coupling agents (Kim, Lee, Kim, & Lee, 2002). The product might be useful in a rapid stimuli-responsive drug delivery system or as a biomimetic actuator in biomedical fields. Similarly, grafting of N-isopropylacrylamide onto sodium alginate with microwave radiation in aqueous environment was carried out to prepare novel pH- and temperature-responsive beads for colon-specific drug delivery (Isiklan & Kucukbalci, 2012).

In addition to the conventional chemical modification approaches to tailor the alginate derivatives, a self-assembly approach has been explored to develop functional multilayer alginate capsules with core-shell structure, which are useful in biomedical applications such as drug delivery, bionanoreactors, nanofiltration, and biosensors (Srivastava & McShane, 2005; Zhu, Srivastava, & McShane, 2005). Partial protonation of the carboxylate groups in alginate chains followed by the cross-linking reaction with cross-linker 2,2'-(ethylenedioxy)-bis(ethylamine) yielded a pH-dependent structure, which could change between a coreshell to a hollow structure depending on the pH change of the medium (Cao et al., 2005). Layer-by-layer self-assembly has been used to prepare microporous alginate hydrogels containing a variety of encapsulates (Roberts, Ritter,

& McShane, 2013). In this approach, a variety of functional materials including sensing element, bioactive agents, and various types of nanoparticles may be encapsulated. A similar multilayer self-assembly approach by coating or depositing with oppositely charged polyelectrolytes bearing complementary amine and acetoacetate reactive groups has also been used to strengthen the alginate microcapsules by internally and externally cross-linked networks, which could become resistant to chemical and mechanical stress while remaining cyto-compatible. The resulting microcapsules are promising materials for cell encapsulation in cell-based therapies (Mazumder, Burke, Shen, Potter, & Stover, 2009; Mazumder, Shen, Burke, Potter, & Stover, 2008; Srivastava & McShane, 2005). Moreover, multilayers could also be built from negatively charged alginate and positively charged chitosan in acid conditions and be used for cell adhesion in tissue engineering applications (Silva et al., 2013a). Other polyelectrolytes such as proteins (β -lactoglobulin or gelatin), poly(L-lysine), and poly(L-ornithine) may also be utilized to form such multilayer structures (Rinaudo, 2008).

4.7. Hyaluronic acid

For diverse biological applications, further chemical modification of HA to introduce desirable properties (e.g. the hydrophobicity and biological activity of resultant materials) is often necessary. In HA, there are three targeting sites per repeating unit available for chemical modifications: carboxylic acid groups; primary and secondary hydroxyl groups; N-acetyl groups. Generally, chemical modifications targeting carboxylic groups include amidation, Ugi condensation, and esterification (Table 2). Carboxylic groups of HA can react either as electrophiles or nucleophiles to form esters (Cumpstey, 2013).

Esterifications of HA by alkylation using alkyl halides (chlorides, iodides, and bromides), by using diazomethane, and by using epoxides have been intensively studied and reviewed previously (Schanté, Zuber, Herlin, & Vandamme, 2011). For example, benzyl ester formation has been used to increase the hydrophobic properties of HA for production of different commercial biocompatible and biodegradable materials (HYAFF®) (Benedetti et al., 1993).

Functionalization targeted at the carboxylic group is similar as that of the alginate and the TEMPO oxidized cellulose modification as described above (Fig. 1 and Fig. 5). Recently Wang, Oommen, Yan, and Varghese (2013) reported a mild and efficient strategy for aldehyde modification of HA by conjugating the amino-glycerol moiety onto the carboxylate residue of HA, which allowed selective cleavage of pendent diol groups without opening of the sugar ring structure of HA during periodate oxidation. This site-selective aldehyde modification could minimize the change of the native structure of HA and preserve its unique physicochemical and biochemical properties. The aldehyde-bearing HA was developed to tailor extracellular matrix injectable hydrogel for growth factor release.

Chemical modifications of HA on the hydroxyl groups (both primary and secondary) mainly include etherification, esterification, hemiacetal crosslinking, carbamate formation, and selective oxidation (Khan & Ahmad, 2013; Schanté et al., 2011).

Modification of the N-acetylglucosamine is difficult to carry out directly, thus deacetylation is often taken to recover the reactive amino groups which are able to conduct amidation or reductive amidation with aldehydes.

When developing HA derivatives for medical and pharmaceutical applications, HA derivatives are categorized as “monolithic”, which are “terminally modified” forms of HA that do not form new chemical bonds in the presence of added cells or molecules, and “living” which can form new covalent bonds in the presence of cells, tissues, and small or large molecules (Prestwich & Kuo, 2008). Living HA crosslinked hydrogels (e.g. crosslinked with poly(ethylene glycol) diacrylate) act as an extracellular matrix and permit incorporation of cells and a wide variety of small molecules, large molecules, nanoparticles, and microparticles, which have broad applications, e.g. targeting specific and long-acting delivery, wound repair, drug evaluation, stem cell niche engineering, and regenerative medicine (Oh et al., 2010; Prestwich, 2007, 2011).

5. Structural analysis

Generally, bioactivities of polysaccharides are highly dependent on their structural features. For example, the anticoagulant activity of seaweed fucans was shown to depend on their molar mass, the extent of sulfation, and the distribution of sulfate groups in the repeating units (Jiao, Yu, Zhang, & Ewart, 2011). Thus, accurately determining and establishing structure–function relationship is the prerequisite and fundament for their applications. Structures of polysaccharides, especially those of heteropolysaccharides or hemicelluloses are complicated by the presence of different monosaccharides used as building blocks, which are usually isobaric stereoisomers, variations in sequence, linkage, branching, and distribution of side chains (Bauer, 2012). Structural elucidation of polysaccharides involves

obtaining data from numerous analytical approaches, each of which gives some structural information, and the assimilation/integration of these data into a chemical structure that rigorously and uniquely fits all the available structural information (Kamerling & Boons, 2007). Thus, several different analytical strategies should be taken for analysis to reach final and accurate conclusions of the polysaccharide structure. Nowadays, the improvements in analytic techniques such as nuclear magnetic resonance (NMR) spectroscopy, high-pressure liquid chromatograph (HPLC), capillary electrophoresis (CE), and mass spectrometry (MS), together with the development of suitable microchemical degradation and derivatization protocols, and the incorporation of exo- and endo-glycosidase digestions, are all greatly contributing to the structural analysis of polysaccharides. Different methodologies available for structural elucidation of polysaccharides have been previously summarized by Kamerling and Boons (2007).

For building the detailed structure of polysaccharides, the primary structural analysis should be carried out to understand the nature and number of the monosaccharides building blocks. This is generally done by hydrolysis and methanolysis followed by gas chromatograph and liquid chromatograph analysis. The absolute configuration (D or L) of the monosaccharides can be determined by separation of enantiomers using gas-liquid chromatograph directly on a chiral stationary phase, or on a nonchiral stationary phase after conversion of the enantiomers into diastereomers using chiral reagent. Linkages between monosaccharides and branch pattern can be analyzed by firstly using methylation analysis, which involves methylation of the free hydroxyl groups, hydrolysis of the methylated glycan, and reduction with NaBH₄ or NaBD₄ and acetylation with acetic anhydride in pyridine, followed by gas-liquid chromatograph separation in combination with mass spectrometric profiling. The following monosaccharides identification can be done by using different mass spectrometry and NMR spectroscopy. Sometimes, modification or degradation (e.g. Smith degradation, uronic acid reduction or degradation, enzymatic and/or partial acid/alkaline hydrolysis, acetolysis, labeling with radioactive or fluorophoric compounds etc.) of polysaccharides are beneficial for constructing the ultimate structures (Kamerling & Boons, 2007; Varki, 2009).

The introduction of soft-ionization techniques in mass spectrometry provides new possibilities for the analysis of polysaccharides. Fast-atom-bombardment MS (FAB MS), matrix-assisted laser-desorption-ionization time-of-flight MS (MALDI TOF MS), and electrospray ionization MS (ESI MS) have become key techniques for identification and molecular mass profiling of polysaccharides present in complex mixtures. Tandem mass (MS/MS) or even MSⁿ spectrometry can give more detailed structural information including sugar constituents, sequence and interresidue linkage positions, and some information on stereochemistry (Mischnick, 2012). To reduce the complexity of the analyte, isolation and profiling of analyte mixtures and even isobaric analytes can be achieved by coupling techniques. For example, conjunction of mass analyzers with different isolation methods, such as reverse-phase, normalphase (NP), porous graphitized carbon, size exclusion, ion exchange, or high performance anion-exchange, liquid chromatographic (LC) or capillary electrophoretic separation methods are all possible

(Maslen, Goubet, Adam, Dupree, & Stephens, 2007; Ungewiß et al., 2005).

However, due to the structural complexity of polysaccharides, no single analytical method alone is able to give the detailed structural information. Collecting structural information from different available techniques such as ultraviolet (UV)/visible (vis) and infrared (IR) absorption spectroscopies, NMR and MS is of significance for accurate elucidation of polysaccharide fine structures.

6. Biomedical applications

Polysaccharides and their derivatives hold advantages over the synthetic polymers, because they are non-toxic, biodegradable, biocompatible, and less expensive compared to their synthetic counterparts. All these merits endow polysaccharides and their derivatives a broad spectrum of applications in different areas, such as in biomedical or pharmaceutical, food, and cosmetic applications. Nowadays, polysaccharides play important roles in traditional disease control and health care (such as those originating from herbs and dietary fibers as reviewed above), meanwhile many new application areas are also explored such as in tissue engineering, in drug delivery, in wound treatment (both internal and external), in cancer prevention, diagnosis, and therapy, and in treatment of bacterial and viral diseases as already mentioned in the previous section for each polysaccharide and their derivatives following functionalization (Khan & Ahmad, 2013; Lindblad, Sjöberg, Albertsson, & Hartman, 2007; Sandra, 2009). Thus, here in this section we emphasize the development of bioactive polysaccharides for such biomedical applications as tissue engineering, wound dressing/healing, and drug delivery applications, which are the three major topics of the most recent research activities.

6.1. Tissue engineering

Exploitation of polysaccharides and their derivatives for tissue engineering applications, such as biological signaling, cell adhesion, cell proliferation, cell differentiation, cell responsive degradation, and re-modeling, is attracting a great deal of interest in medical research for guiding and promoting new tissue regeneration or to define the shape and structure of cell growth (Khan & Ahmad, 2013). A variety of polysaccharides, such as alginate, chitin, chitosan, hyaluronic acid, cellulose, chondroitin sulfate, starch and their derivatives, have been developed as biomaterials for tissue engineering applications as reviewed above and previously elsewhere (Oliveira & Reis, 2011). Application of polysaccharides as scaffolds in tissue engineering needs to fulfill the requirements like biocompatibility and nontoxicity, biodegradability with controllable degradation rate, appropriate porosity, and structural integrity (Khan & Ahmad, 2013).

Chitin and chitosan possess the requisite properties to act as scaffolds for tissue engineering, with respect to their degradability, immunogenicity, and mechanical strength, and therefore have been developed for tissue engineering applications in the form of 3D hydrogels or porous sponges, fibrous scaffolds or free-standing films, within which the appropriate

cell types are seeded for *in vitro* or *in vivo* culture and evaluation (Wan & Tai, 2013). Design of 3D chitin/chitosan hydrogel and sponge scaffolds, or 2D scaffolds and free-stand films to support cartilage regeneration, to chemically interact with apatite for bone and tendon regeneration, to encapsulate stem cells and support their growth and differentiation for different stem cell therapy, and their utility in regenerative medicine have been recently reported and reviewed elsewhere (Croisier & Jérôme, 2013; Lu et al., 2012; Lu et al., 2012; Suh & Matthew, 2000; Wu & Hochedlinger, 2011). Moreover, composites of chitosan with hydroxyapatite and grafted chitosan with carbon nanotubes have been developed as potential materials for artificial bone and bone regeneration in tissue engineering (Venkatesan & Kim, 2010). Other polysaccharide-based materials, such as, hyaluronic acid, starch, and cellulose, have also been explored for bone, cartilage, and/or skin tissue engineering applications (Rinaudo, 2008).

6.2. Wound healing and wound dressing

Due to their inherent biocompatibility, low toxicity, and pharmaceutical biomedical activity, various polysaccharides, such as chitin, chitosan, cellulose, hyaluronan, and alginate, have been widely used to prepare wound healing materials (Barud Hda et al., 2013; Czaja, Krystynowicz, Bielecki, & Brown, 2006; Czaja, Young, Kawecki, & Brown, 2007; Hrynuk, Martins-Green, Barron, & Neufeld, 2012). For example, hyaluronan, a major extracellular component with unique hygroscopic, rheological, and viscoelastic properties, has been extensively developed for tissue repair purposes due to its physicochemical properties and specific interactions with cells and extracellular matrix. It is generally accepted that hyaluronan plays multifaceted roles in the mediation of the tissue repair process and is involved in all the stages of wound healing, i.e. inflammation, granulation tissue formation, reepithelialization, and remodeling. Derivatives of hyaluronan, such as cross-linked, esterified or other chemically modified products have also been developed for tissue repair or wound healing purposes (Anilkumar et al., 2011; Chen & Abatangelo, 1999). Notably, wound healing-promoting activity of the materials is also important in the designing of materials for tissue engineering.

All-natural composite wound dressing films prepared by dispersion and encapsulation of essential oils (elicriso italic, chamomile blue, cinnamon, lavender, tea tree, peppermint, eucalyptus, lemongrass, and lemon oils) in sodium alginate matrices have been reported to show remarkable antimicrobial and antifungal properties and may find application as disposable wound dressings (Liakos et al., 2013). Chitosan/silk fibroin blending membranes crosslinked with dialdehyde alginate have been developed for wound dressing and the membranes were found to promote the cell attachment and proliferation, which suggests a promising candidate for wound healing applications (Gu, Xie, Huang, Li, & Yu, 2013). Blending aqueous dispersions of sodium alginate and povidone iodine (PVPI) complex was prepared as freestanding NaAlg films or as Ca^{2+} -cross-linked alginate beads. These products were demonstrated to show antibacterial and antifungal activity and controlled release of PVPI into open wounds when the composite films and beads were brought into direct contact with water or with moist media (Liakos

et al., 2013). This proved that they could be suitable for therapeutic applications such as wound dressings. *In situ* injectable nano-composite hydrogels composed of curcumin, N,O-carboxymethyl chitosan, and oxidized alginate as a novel wound dressing was successfully developed for dermal wound repair application (Li et al., 2012b). *In vitro* release, *in vivo* wound healing, and histological studies all suggested that the developed nano-curcumin/N,O-carboxymethyl chitosan/oxidized alginate hydrogel as a promising wound dressing might have a potential application in the wound healing. Silver nanoparticles containing polyvinyl pyrrolidone and alginate hydrogels were synthesized using gamma radiation and showed the ability of preventing fluid accumulation in exuding wound (Singh & Singh, 2012). The incorporation of nanosilver particles provided a strong antimicrobial effect and therefore made such polyvinyl pyrrolidone/alginate hydrogels suitable for use as wound dressing. Except the alginate and its various derivatives, other natural polysaccharides such as cellulose, chitin, chitosan, and hyaluronic acid have also been explored for wound dressing or wound healing applications (Anisha, Biswas, Chennazhi, & Jayakumar, 2013; Kondo, Niiyama, Yu, & Kuroyanagi, 2011; Matsumoto & Kuroyanagi, 2010).

6.3. Drug delivery and controlled release

Polysaccharides hold their promising potential in drug delivery and controlled release applications due to their advantages such as biocompatibility, low immunogenicity, and minimal cytotoxicity. Numerous polysaccharide-based drug delivery systems have been developed for specific targeting delivery or controlling release, for protection of drugs from premature degradation, for improving intracellular penetration and transporation, for enhancing stability and bioavailability of drugs, or for the delivery of biomolecules such as genes, antigens, and small interfering RNA (Csaba, Koping-Hoggard, & Alonso, 2009; Mao, Sun, & Kissel, 2010; Mizrahy & Peer, 2012; Valo et al., 2011). These delivery systems are generally prepared in the form of 3-D cross-linking network (covalently or ionically crosslinking), the polyelectrolyte structures (polyelectrolyte complexes or layer-by-layer assembly), self-assembly, and the polysaccharides-drug conjugate (Mizrahy & Peer, 2012). The release of the entrapped drugs or certain molecules can be triggered by the change of pH, ions, electrical or magnetic field, light, temperature, redox potential, or certain molecules (Alvarez-Lorenzo, Blanco-Fernandez, Puga, & Concheiro, 2013). Cellulose, chitin or chitosan, and alginate, representing the three most abundant polysaccharide types, are discussed more in detail below.

Pharmaceutical utilization of cellulose and its derivatives range from excipients through carriers and protecting agents to active substances themselves. Oral drug delivery is one of those applications, in which the polysaccharide excipients are used to increase the solubility and bioavailability of the active drugs, to achieve a certain release profile from the final formulation, and to enhance the stability of the final drug products (Marchessault, Ravenelle, & Zhu, 2006; Reddy, Mohan, Satla, & Gaikwad, 2011). Nowadays, cellulose (e.g. microcrystalline cellulose) and starch (e.g. corn and rice starch) are widely used as glidants, tablet disintegrants and binders,

and capsule diluents (Marchessault et al., 2006). Numerous cellulose derivatives such as methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose, which often possess specific respond or even better physicochemical properties than cellulose have been applied in pharmaceutical applications (Francis, Piredda, & Winnik, 2006; Jain et al., 2014; Li & Mei, 2006; Marchessault et al., 2006). For example, phthalated hydroxypropylmethyl cellulose has excellent pH-dependent solubility, namely, stability in acidic conditions (at stomach) but soluble in mildly acidic to slightly alkaline solution and, therefore, has been developed for controlled intestinal targeting drug release systems (Kim, Park, Cheong, & Kim, 2003; Xu, Gao, Xu, Wu, & Sun, 2009). Recently, drug delivery systems based on nanocellulose which including cellulose nanocrystals (CNCs), nanofibrillated cellulose (NFC), and bacterial cellulose (BC) have been explored extensively (Plackett, Letchford, JacksonJohn, & Burt, 2014). For example, antimicrobials (doxorubicin hydrochloride and tetracycline hydrochloride) binding to and release from CNCs have been tested based on the ionically crosslinking delivery system, in which negatively charged sulfate groups on the CNCs form reversible ionic crosslinking with the positively charged drugs (Jackson et al., 2011). Similarly, NFC film networks have been studied to entrap drugs and used for long lasting drug release, for example the entrapped poorly water soluble drugs in the NFC film networks can sustainably release over weeks (e.g. indomethacin, 1–2 weeks) or even months (e.g. beclomethasone dipropionate and itraconazole, 3 months) (Kolakovic, Peltonen, Laukkanen, Hirvonen, & Laaksonen, 2012). Highly porous nanocellulose aerogels ($\epsilon=90\text{--}99\%$) with large surface areas ($S_a=70\text{--}680\text{ m}^2/\text{g}$) prepared by freeze-drying may provide new possibilities for enhancing drug bioavailability and drug loading capacity (García-González et al., 2011). For example aerogels of BC (Valo et al., 2013) or NFC (Valo et al., 2011) have been studied for stabilizing and release of insoluble drugs within nanoparticle formulations in a controlled manner.

Exploring the use of chitin or chitosan as biomolecular delivery vector is of increasing interest in drug delivery for therapeutic application, such as genes (Csaba et al., 2009), antigens (Chen, Huang, Lai, & Ling, 2013), small interfering RNA carrier (siRNA) (Mao, Sun, & Kissel, 2010), and cells and proteins (Shelke, James, Laurencin, & Kumbar, 2014). Application of chitosan-based siRNA carrier for efficient delivery of siRNA *in vivo* has shown great promise as a therapeutic tool for gene expression implicated disease (Ragelle, Vandermeulen, & Preat, 2013). For example the chitosan (Ji et al., 2009) has been directly used to prepare chitosan/siRNA nanoparticles which showed knockdown human colorectal cancer gene expression. Alternative, Katas and Alpar (2006) found that the chitosan/siRNA nanoparticles which were prepared by ionic gelation with sodium tripolyphosphate showed much higher target gene silencing effect due to the higher binding and loading efficiency. Tahara, Yamamoto, Hirashima, and Kawashima (2010) proved that the chitosan coating of the nanocapsules can protect the encapsulated siRNA from the degradation by nucleases meanwhile avoid the burst release of siRNA. Extended delivery of encapsulated antigens or intradermal vaccines to the skin via a chitosan microneedle transdermal delivery system has been reported to provide sustained immune stimulation (Chen, Huang, Lai & Ling, 2013).

Cross-linking of alginate with di- and tri-valent ions (Ca, Ba, Sr, Al) to form the reversible “egg-box” array has been exploited to prepare pH-responsive network for intestinal target drug delivery (Alvarez-Lorenzo et al., 2013). Such pH-responsive is based on the limited swelling in the acidic environment (pH 1.2) in stomach and erosion of the network in the neutral environment (pH 7–7.4) in intestine. However, such pH sensitivity can also result in the stability problem of the delivery system (Mizrahy & Peer, 2012). Alternatively, various alginate and hyaluronic acid (semi-) interpenetrating polymer networks ((semi-)IPNs) have been developed for the application in drug delivery systems as reviewed by Matricardi, Di Meo, Coviello, Hennink, and Alhaique (2013). In addition to the pH-responsive network, the temperature-responsive alginate (semi-)IPNs delivery system has been explored by incorporation of poly(N-isopropylacrylamide); by physically or chemically crosslinking via the addition of Ca^{2+} and N,N'-methylenebisacrylamide respectively; and by photopolymerization via incorporation of photoinitiator, such as 2-hydroxy-1-[4-(2-hydroxyethoxy)phenyl]-2-methyl-1-propanone (Matricardi et al., 2013).

Several other polysaccharides such as pectin, chitin, chitosan, guar gum, xanthan gum, gellan gum, dextran, and chondroitin have also been developed for drug delivery or controlled drug release, which were reviewed in the functionalization of polysaccharides section in this paper and somewhere else by others (Liu, Jiao, Wang, Zhou, & Zhang, 2008; Luo & Wang, 2013; Morris, Kok, Harding, & Adams, 2010; Pachau & Mazumder, 2013; Reddy et al., 2011; Tonnesen & Karlsen, 2002; Zhang et al., 2013b).

7. Concluding remarks and outlook

Polysaccharides have received considerable attention as functional biomaterials for novel and highly value-added applications, such as pharmaceutical, biomedical, and cosmetic applications owing to their non-toxic, biocompatible, and biodegradable properties. Proper isolation of native bioactive polysaccharides from various sources and determination of their structural features enable a clear understanding of the mechanism of biological action and structure–activity relationships. These in turn will facilitate the biomimic structural modification or functionalization of non-bioactive polysaccharides towards similar or more desirable bioactivities. However, how to isolate the bioactive polysaccharides with high purity and in large amount, meanwhile preserving their native structure remains a demanding and important task for future research. Various chemical modification approaches, such as partial hydrolysis, oxidation, reduction, etherification, esterification, and cross-linking, are available for tailoring the polysaccharides with desired properties. However, the presence of different monosaccharides used as building blocks, which usually are isobaric stereoisomers, variations in sequence, linkage, branching, and distribution of side chains, and functional groups after modifications result in a wide structural diversity of polysaccharides. This not only leads to the uncertainty or less specificity of the chemical modification to some extent, but also brings challenges to determine and establish the structure–function relationships that are the prerequisite and foundation for their applications. Enzymatic modifications are valuable tools for targeted functionalization of polysaccharides

with high specificity; therefore, combining enzymatic and chemical approaches may offer an excellent alternative to engineer the properties of polysaccharides in a controlled manner. Proper isolation and purification of the chemically functionalized or natively bioactive polysaccharides is of crucial importance for applications in the biomedical area, as there is a need to avoid the undesirable side reactions of by-products, remainants of solvents and impurities in the products, and thus to enable the safe, reproducible and accurate dosage for experimental or therapeutic applications. Accumulating data from different modern structural analysis techniques, such as ultraviolet and infrared absorption spectroscopic, mass spectrometry, nuclear magnetic resonance spectroscopy, and some hyphenated approaches (HPLC–MS, HPLC–NMR, HPLC–DAD–MS–NMR, HPLC–TOF–MSⁿ, etc.) may enable a clear determination of structural features of the functionalized polysaccharides. The successful outcome of exploitation of polysaccharides in biomedical applications will require multidisciplinary expertise in plant biology, organic chemistry, material science and engineering, medical, health care and beyond.

Acknowledgements

Jun Liu would like to acknowledge the financial support of the China Scholarship Council. This work is part of the activities in the Graduate School of Chemical Engineering and also of the activities in the Åbo Akademi University Process Chemistry Centre.

REFERENCES

- Aachary, A. A., & Prapulla, S. G. (2011). Xylooligosaccharides (XOS) as an emerging prebiotic: Microbial synthesis, utilization, structural characterization, bioactive properties, and applications. *Comprehensive Reviews in Food Science and Food Safety*, 10(1), 2–16.
- Abe, M., Fukaya, Y., & Ohno, H. (2010). Extraction of polysaccharides from bran with phosphonate or phosphinate-derived ionic liquids under short mixing time and low temperature. *Green Chemistry*, 12(7), 1274–1280.
- Al-Ghazzewi, F. H., Khanna, S., Tester, R. F., & Piggott, J. (2007). The potential use of hydrolysed konjac glucomannan as a prebiotic. *Journal of the Science of Food and Agriculture*, 87(9), 1758–1766.
- Alliston, T. (2010). Chondroitin sulfate and growth factor signaling in the skeleton: Possible links to MPS VI. *Journal of Pediatric Rehabilitation Medicine*, 3(2), 129–138.
- Alonso-Sande, M., Teijeiro-Orsorio, D., Remunan-Lopez, C., & Alonso, M. J. (2009). Glucosaminan, a promising polysaccharide for biopharmaceutical purposes. *European Journal of Pharmaceutics and Biopharmaceutics*, 72(2), 453–462.
- Alvarez-Lorenzo, C., Blanco-Fernandez, B., Puga, A. M., & Concheiro, A. (2013). Crosslinked ionic polysaccharides for stimuli-sensitive drug delivery. *Advanced Drug Delivery Reviews*, 65(9), 1148–1171.
- Alves, N. M., & Mano, J. F. (2008). Chitosan derivatives obtained by chemical modifications for biomedical and environmental applications. *International Journal of Biological Macromolecules*, 43(5), 401–414.
- An, H. J., & Lebrilla, C. B. (2011). Structure elucidation of native N- and O-linked glycans by tandem mass spectrometry (tutorial). *Mass Spectrometry Reviews*, 30(4), 560–578.

- Anderson, J. W., Baird, P., Davis, R. H., Jr., Ferreri, S., Knudtson, M., Koraym, A., Waters, V., & Williams, C. L. (2009). Health benefits of dietary fiber. *Nutrition Reviews*, 67(4), 188–205.
- Anilkumar, T. V., Muhamed, J., Jose, A., Jyothi, A., Mohanan, P. V., & Krishnan, L. K. (2011). Advantages of hyaluronic acid as a component of fibrin sheet for care of acute wound. *Biologicals*, 39(2), 81–88.
- Anisha, B. S., Biswas, R., Chennazhi, K. P., & Jayakumar, R. (2013). Chitosan-hyaluronic acid/nano silver composite sponges for drug resistant bacteria infected diabetic wounds. *International Journal of Biological Macromolecules*, 62, 310–320.
- Araki, J., Wada, M., & Kuga, S. (2000). Steric stabilization of a cellulose microcrystal suspension by poly(ethylene glycol) grafting. *Langmuir*, 17(1), 21–27.
- Arola, S., Tammelin, T., Setälä, H., Tullila, A., & Linder, M. B. (2012). Immobilization-stabilization of proteins on nanofibrillated cellulose derivatives and their bioactive film formation. *Biomacromolecules*, 13(3), 594–603.
- Athukorala, Y., Ahn, G., Jee, Y.-H., Kim, G.-Y., Kim, S.-H., Ha, J.-H., Kang, J.-S., Lee, K.-W., & Jeon, Y.-J. (2009). Antiproliferative activity of sulfated polysaccharide isolated from an enzymatic digest of *Ecklonia cava* on the U-937 cell line. *Journal of Applied Phycology*, 21(3), 307–314.
- Baek, S. H., Lee, J. G., Park, S. Y., Bae, O. N., Kim, D. H., & Park, J. H. (2010). Pectic polysaccharides from *Panax ginseng* as the antirotavirus principals in ginseng. *Biomacromolecules*, 11(8), 2044–2052.
- Baier, G., Baumann, D., Siebert, J. M., Musyanovych, A., Mailander, V., & Landfester, K. (2012). Suppressing unspecific cell uptake for targeted delivery using hydroxyethyl starch nanocapsules. *Biomacromolecules*, 13(9), 2704–2715.
- Balazs, E. (2009). Therapeutic use of hyaluronan. *Structural Chemistry*, 20(2), 341–349.
- Barnhill, J., Fye, C., Williams, D., Reda, D., Harris, C., & Clegg, D. (2006). Chondroitin product selection for the glucosamine/chondroitin arthritis intervention trial. *Journal of American Pharmacists Association*(2003), 46(1), 14–24.
- Bartnicki-Garcia, S. (1968). Cell wall chemistry, morphogenesis, and taxonomy of fungi. *Annual Review of Microbiology*, 22, 87–108.
- Barud Hda, S., de Araujo Junior, A. M., Saska, S., Mestieri, L. B., Campos, J. A., de Freitas, R. M., Ferreira, N. U., Nascimento, A. P., Miguel, F. G., Vaz, M. M., Barizon, E. A., Marquede-Oliveira, F., Gaspar, A. M., Ribeiro, S. J., & Berretta, A. A. (2013). Antimicrobial Brazilian propolis (EPP-AF) containing biocellulose membranes as promising biomaterial for skin wound healing. *Evidence-based Complementary and Alternative Medicine*, 2013, 703024.
- Bashar, A. S., Khan, M. A., & Idriss Ali, K. M. (1995). Modification of cotton, rayon and silk fibers by radiation induced graft copolymerization. *Radiation Physics and Chemistry*, 45(5), 753–759.
- Bauer, S. (2012). Mass spectrometry for characterizing plant cell wall polysaccharides. *Frontiers in Plant Science*, 3, 45.
- BeMiller, J. N., & Whistler, R. L. (2009). *Starch: Chemistry and technology*. Boston: Academic.
- Benedetti, L., Cortivo, R., Berti, T., Berti, A., Pea, F., Mazzo, M., Moras, M., & Abatangelo, G. (1993). Biocompatibility and biodegradation of different hyaluronan derivatives (Hyaff) implanted in rats. *Biomaterials*, 14(15), 1154–1160.
- Berg, J. M., Tymoczko, J. L., & Stryer, L. (2012). *Biochemistry*. New York, NY: W.H. Freeman.
- Besheer, A., Hause, G., Kressler, J., & Mader, K. (2007). Hydrophobically modified hydroxyethyl starch: Synthesis, characterization, and aqueous self-assembly into nano-sized polymeric micelles and vesicles. *Biomacromolecules*, 8(2), 359–367.
- Bhattacharya, M., Malinen, M. M., Lauren, P., Lou, Y. R., Kuisma, S. W., Kanninen, L., Lille, M., Corlu, A., GuGuen-Guillouzo, C., Ikkala, M., Laukkanen, A., Urtti, A., & Yliperttula, M. (2012). Nanofibrillar cellulose hydrogel promotes three-dimensional liver cell culture. *Journal of Controlled Release*, 164(3), 291–298.
- Biliuta, G., Fras, L., Drobota, M., Persin, Z., Kreze, T., Stana-Kleinschek, K., Ribitsch, V., Harabagiu, V., & Coseri, S. (2013). Comparison study of TEMPO and phthalimide-N-oxyl (PINO) radicals on oxidation efficiency toward cellulose. *Carbohydrate Polymers*, 91(2), 502–507.
- Bird, A. R., Conlon, M. A., Christophersen, C. T., & Topping, D. L. (2010). Resistant starch, large bowel fermentation and a broader perspective of prebiotics and probiotics. *Beneficial Microbes*, 1(4), 423–431.
- Bouhadir, K. H., Lee, K. Y., Alsberg, E., Damm, K. L., Anderson, K. W., & Mooney, D. J. (2001). Degradation of partially oxidized alginate and its potential application for tissue engineering. *Biotechnology Progress*, 17(5), 945–950.
- Brown, L., Rosner, B., Willett, W. W., & Sacks, F. M. (1999). Cholesterol-lowering effects of dietary fiber: A meta-analysis. *American Journal of Clinical Nutrition*, 69(1), 30–42.
- Brumer, H., Zhou, Q., Baumann, M. J., Carlsson, K., & Teeri, T. T. (2004). Activation of crystalline cellulose surfaces through the chemoenzymatic modification of xyloglucan. *Journal of the American Chemical Society*, 126(18), 5715–5721.
- Bulpitt, P., & Aeschlimann, D. (1999). New strategy for chemical modification of hyaluronic acid: Preparation of functionalized derivatives and their use in the formation of novel biocompatible hydrogels. *Journal of Biomedical Materials Research*, 47(2), 152–169.
- Cai, K., Yao, K., Li, Z., Yang, Z., & Li, X. (2001). Rat osteoblast functions on the o-carboxymethyl chitosan-modified poly(D,L-lactic acid) surface. *Journal of Biomaterials Science Polymer Edition*, 12(12), 1303–1315.
- Calvini, P., Gorassini, A., Luciano, G., & Franceschi, E. (2006). FTIR and WAXS analysis of periodate oxycellulose: Evidence for a cluster mechanism of oxidation. *Vibrational Spectroscopy*, 40(2), 177–183.
- Cancilla, M. T., Penn, S. G., & Lebrilla, C. B. (1998). Alkaline degradation of oligosaccharides coupled with matrix-assisted laser desorption/ionization Fourier transform mass spectrometry: A method for sequencing oligosaccharides. *Analytical Chemistry*, 70(4), 663–672.
- Cao, Y., & Ikeda, I. (2009). Antioxidant activity and antitumor activity (in vitro) of xyloglucan selenious ester and surfated xyloglucan. *International Journal of Biological Macromolecules*, 45(3), 231–235.
- Cao, Y., Shen, X., Chen, Y., Guo, J., Chen, Q., & Jiang, X. (2005). pH-induced self-assembly and capsules of sodium alginate. *Biomacromolecules*, 6(4), 2189–2196.
- Capriles, V. D., & Areas, J. A. (2013). Effects of prebiotic inulin-type fructans on structure, quality, sensory acceptance and glycemic response of gluten-free breads. *Food & Function*, 4(1), 104–110.
- Caridade, S. G., Monge, C., Gilde, F., Boudou, T., Mano, J. F., & Picart, C. (2013). Free-standing polyelectrolyte membranes made of chitosan and alginate. *Biomacromolecules*, 14(5), 1653–1660.
- Casiglia, E., Tikhonoff, V., Caffi, S., Boschetti, G., Grasselli, C., Saugo, M., Giordano, N., Rapisarda, V., Spinella, P., & Palatini, P. (2013). High dietary fiber intake prevents stroke at a population level. *Clinical Nutrition*, 32(5), 811–818.
- Chao, Z., Ri-fu, Y., & Tai-qiu, Q. (2013). Ultrasound-enhanced subcritical water extraction of polysaccharides from *Lycium barbarum* L. *Separation and Purification Technology*, 120(0), 141–147.
- Chappell, E. P., & Liu, J. (2013). Use of biosynthetic enzymes in heparin and heparan sulfate synthesis. *Bioorganic and Medicinal Chemistry*, 21(16), 4786–4792.
- Charlton, K. E., Tapsell, L. C., Batterham, M. J., O'Shea, J., Thorne, R., Beck, E., & Tosh, S. M. (2012). Effect of 6 weeks' consumption of

- beta-glucan-rich oat products on cholesterol levels in mildly hypercholesterolaemic overweight adults. *British Journal of Nutrition*, 107(7), 1037–1047.
- Chattopadhyay, N., Ghosh, T., Sinha, S., Chattopadhyay, K., Karmakar, P., & Ray, B. (2010). Polysaccharides from *Turbinaria conoides*: Structural features and antioxidant capacity. *Food Chemistry*, 118(3), 823–829.
- Chau, C. F., Huang, Y. L., & Lin, C. Y. (2004). Investigation of the cholesterol-lowering action of insoluble fibre derived from the peel of *Citrus sinensis* L. cv. Liucheng. *Food Chemistry*, 87(3), 361–366.
- Chawla, R., & Patil, G. R. (2010). Soluble dietary fiber. *Comprehensive Reviews in Food Science and Food Safety*, 9(2), 178–196.
- Chen, J., & Raymond, K. (2008). Beta-glucans in the treatment of diabetes and associated cardiovascular risks. *Vascular Health and Risk Management*, 4(6), 1265–1272.
- Chen, M. C., Huang, S. F., Lai, K. Y., & Ling, M. H. (2013). Fully embeddable chitosan microneedles as a sustained release depot for intradermal vaccination. *Biomaterials*, 34(12), 3077–3086.
- Chen, R., Liu, Z., Zhao, J., Chen, R., Meng, F., Zhang, M., & Ge, W. (2011). Antioxidant and immunobiological activity of water-soluble polysaccharide fractions purified from *Acanthopanax senticosu*. *Food Chemistry*, 127(2), 434–440.
- Chen, S., Chen, H., Tian, J., Wang, J., Wang, Y., & Xing, L. (2014). Enzymolysis-ultrasonic assisted extraction, chemical characteristics and bioactivities of polysaccharides from corn silk. *Carbohydrate Polymers*, 101, 332–341.
- Chen, W. Y., & Abatangelo, G. (1999). Functions of hyaluronan in wound repair. *Wound Repair and Regeneration*, 7(2), 79–89.
- Cheng, H., Feng, S., Jia, X., Li, Q., Zhou, Y., & Ding, C. (2013). Structural characterization and antioxidant activities of polysaccharides extracted from *Epimedium acuminatum*. *Carbohydrate Polymers*, 92(1), 63–68.
- Cherbut, C. (2002). Inulin and oligofructose in the dietary fibre concept. *British Journal of Nutrition*, 87(S2), S159–S162.
- Colegate, S. M., & Molyneux, R. J. (2008). *Bioactive natural products: Detection, isolation, and structural determination*. Boca Raton, FL: CRC Press.
- Cooke, C. L., An, H. J., Kim, J., Solnick, J. V., & Lebrilla, C. B. (2007). Method for profiling mucin oligosaccharides from gastric biopsies of rhesus monkeys with and without *Helicobacter pylori* infection. *Analytical Chemistry*, 79(21), 8090–8097.
- Coseri, S., Nistor, G., Frasc, L., Strnad, S., Harabagiu, V., & Simionescu, B. C. (2009). Mild and selective oxidation of cellulose fibers in the presence of N-hydroxyphthalimide. *Biomacromolecules*, 10(8), 2294–2299.
- Coviello, T., Matricardi, P., & Alhaique, F. (2006). Drug delivery strategies using polysaccharidic gels. *Expert Opinion on Drug Delivery*, 3(3), 395–404.
- Crescenzi, V., Francescangeli, A., Capitani, D., Mannina, L., Renier, D., & Bellini, D. (2003). Hyaluronan networking via Ugi's condensation using lysine as cross-linker diamine. *Carbohydrate Polymers*, 53(3), 311–316.
- Crini, G. (2005). Recent developments in polysaccharide-based materials used as adsorbents in wastewater treatment. *Progress in Polymer Science*, 30(1), 38–70.
- Croisier, F., & Jérôme, C. (2013). Chitosan-based biomaterials for tissue engineering. *European Polymer Journal*, 49(4), 780–792.
- Csaba, N., Koping-Hoggard, M., & Alonso, M. J. (2009). Ionically crosslinked chitosan/tripolyphosphate nanoparticles for oligonucleotide and plasmid DNA delivery. *International Journal of Pharmaceutics*, 382(1–2), 205–214.
- Cumpstey, I. (2013). Chemical modification of polysaccharides. *ISRN Organic Chemistry*, 2013, 417672.
- Czaja, W., Krystynowicz, A., Bielecki, S., & Brown, R. M., Jr. (2006). Microbial cellulose—The natural power to heal wounds. *Biomaterials*, 27(2), 145–151.
- Czaja, W. K., Young, D. J., Kawecki, M., & Brown, R. M., Jr. (2007). The future prospects of microbial cellulose in biomedical applications. *Biomacromolecules*, 8(1), 1–12.
- D'Ayala, G. G., Malinconico, M., & Laurienzo, P. (2008). Marine derived polysaccharides for biomedical applications: Chemical modification approaches. *Molecules*, 13(9), 2069–2106.
- Dahou, W., Ghemati, D., Oudia, A., & Aliouche, D. (2010). Preparation and biological characterization of cellulose graft copolymers. *Biochemical Engineering Journal*, 48(2), 187–194.
- Dan, R., Wang, Y., Du, L., Du, S., Huang, M., Yang, S., & Zhang, M. (2013). The synthesis of molecular imprinted chitosan-gels copolymerized with multiform functional monomers at three different temperatures and the recognition for the template ovalbumin. *Analyst*, 138(12), 3433–3443.
- Doctor, V. M., & Sauls, V. (1983). Isolation and anticoagulant properties of a new sulfated xylan: Comparison with heparin and a sodium pentosan polysulfate (SP-54). *Thrombosis Research*, 30(6), 573–578.
- Doliška, A., Willför, S., Strnad, S., Ribitsch, V., Kleinschek, K. S., Eklund, P., & Xu, C. (2012). Antithrombotic properties of sulfated wood-derived galactoglucomannans. *Holzforschung*, 66, 149.
- Dong, H., Snyder, J. F., Tran, D. T., & Leadore, J. L. (2013). Hydrogel, aerogel and film of cellulose nanofibrils functionalized with silver nanoparticles. *Carbohydrate Polymers*, 95(2), 760–767.
- Dong, J.-Z., Wang, Z.-C., & Wang, Y. (2011). Rapid extraction of polysaccharides from fruits of *Lycium barbarum* L. *Journal of Food Biochemistry*, 35(4), 1047–1057.
- Dube, D. H., & Bertozzi, C. R. (2005). Glycans in cancer and inflammation—Potential for therapeutics and diagnostics. *Nature Reviews Drug Discovery*, 4(6), 477–488.
- Ebringerová, A., & Heinze, T. (2000). Xylan and xylan derivatives—Biopolymers with valuable properties. 1. Naturally occurring xyans structures, isolation procedures and properties. *Macromolecular Rapid Communications*, 21(9), 542–556.
- Ebringerová, A., Hromádková, Z., Hřibálová, V., Xu, C., Holmbom, B., Sundberg, A., & Willför, S. (2008). Norway spruce galactoglucomannans exhibiting immunomodulating and radical-scavenging activities. *International Journal of Biological Macromolecules*, 42(1), 1–5.
- Edgar, K. J., Heinze, T., & Buchanan, C. M. (2009). *Polysaccharide materials performance by design*. ACS symposium series (p. 1017). Washington, DC: American Chemical Society1017.
- FAO. Home page. Website: (<http://www.fao.org>).
- Fares, M. M., Assaf, S. M., & Abul-Haija, Y. M. (2010). Pectin grafted poly(N-vinylpyrrolidone): Optimization and in vitro controllable theophylline drug release. *Journal of Applied Polymer Science*, 117(4), 1945–1954.
- Francis, M. F., Piredda, M., & Winnik, F. M. (2006). *Hydroxypropylcellulose in oral drug delivery*. Polysaccharides for drug delivery and pharmaceutical applications, Vol. 934. American Chemical Society57–75.
- Fraser-Reid, B. O., Tatsuta, K., & Thiem, J. (2008). *Glycoscience chemistry and chemical biology* (v. xxxii, 2874 p.). Berlin; New York: Springer3.
- Fu, G., Zhao, J., Yu, H., Liu, L., & He, B. (2007). Bovine serum albumin-imprinted polymer gels prepared by graft copolymerization of acrylamide on chitosan. *Reactive and Functional Polymers*, 67(5), 442–450.
- Fuentes-Zaragoza, E., Riquelme-Navarrete, M. J., Sánchez-Zapata, E., & Pérez-Álvarez, J. A. (2010). Resistant starch as functional ingredient: A review. *Food Research International*, 43(4), 931–942.
- Gaffney, J., Matou-Nasri, S., Grau-Olivares, M., & Slevin, M. (2010). Therapeutic applications of hyaluronan. *Molecular Biosystems*, 6(3), 437–443.
- Gao, C., Liu, M., Chen, S., Jin, S., & Chen, J. (2009). Preparation of oxidized sodium alginate-graft-poly((2-dimethylamino) ethyl methacrylate) gel beads and in vitro controlled release

- behavior of BSA. *International Journal of Pharmaceutics*, 371(1–2), 16–24.
- García-González, C. A., Alnaief, M., & Smirnova, I. (2011). Polysaccharide-based aerogels—Promising biodegradable carriers for drug delivery systems. *Carbohydrate Polymers*, 86(4), 1425–1438.
- Gatenholm, P., & Tenkanen, M. (2004). *Hemicelluloses: Science and technology*. Washington, DC, New York: American Chemical Society; Distributed by Oxford University Press.
- Gatti, G., Casu, B., Hamer, G. K., & Perlin, A. S. (1979). Studies on the conformation of heparin by ^1H and ^{13}C NMR spectroscopy. *Macromolecules*, 12(5), 1001–1007.
- Ghosh, P., Adhikari, U., Ghosal, P. K., Pujol, C. A., Carlucci, M. J., Damonte, E. B., & Ray, B. (2004). In vitro anti-herpetic activity of sulfated polysaccharide fractions from *Caulerpa racemosa*. *Phytochemistry*, 65(23), 3151–3157.
- Gidley, M. J., Lillford, P. J., Rowlands, D. W., Lang, P., Dentini, M., Crescenzi, V., Edwards, M., Fanutti, C., & Reid, J. S. (1991). Structure and solution properties of tamarind-seed polysaccharide. *Carbohydrate Research*, 214(2), 299–314.
- Grote, C., & Heinze, T. (2005). Starch derivatives of high degree of functionalization 11: Studies on alternative acylation of starch with long-chain fatty acids homogeneously in *N,N*-dimethyl acetamide/LiCl. *Cellulose*, 12(4), 435–444.
- Gu, Z., Xie, H., Huang, C., Li, L., & Yu, X. (2013). Preparation of chitosan/silk fibroin blending membrane fixed with alginate dialdehyde for wound dressing. *International Journal of Biological Macromolecules*, 58, 121–126.
- Haaksman, I. K., Besemer, A. C., Jetten, J. M., Timmermans, J. W., & Slaghek, T. M. (2006). The oxidation of the aldehyde groups in dialdehyde starch. *Starch-Stärke*, 58(12), 616–622.
- Harhaji Trajkovic, L. M., Mijatovic, S. A., Maksimovic-Ivanic, D. D., Stojanovic, I. D., Momcilovic, M. B., Tufegdizic, S. J., Maksimovic, V. M., Marjanovic, Z. S., & Stosic-Grujicic, S. D. (2009). Anticancer properties of *Ganoderma lucidum* methanol extracts in vitro and in vivo. *Nutrition and Cancer*, 61(5), 696–707.
- Harlev, E., Nevo, E., Lansky, E. P., Ofir, R., & Bishayee, A. (2012). Anticancer potential of aloes: Antioxidant, antiproliferative, and immunostimulatory attributes. *Planta Medica*, 78(9), 843–852.
- Hartmans, S., de Vries Hielke, T., Beijer, P., Brady Richard, L., Hofbauer, M., & Haandrikman Alfred, J. (2003). *Production of oxidized guar galactomannan and its applications in the paper industry*. *Hemicelluloses: Science and technology*, Vol. 864. American Chemical Society 360–371.
- Hata, H., Onishi, H., & Machida, Y. (2000). Preparation of CM-chitin microspheres by complexation with iron(III) in w/o emulsion and their biodisposition characteristics in mice. *Biomaterials*, 21(17), 1779–1788.
- Heinze, T. (2005). *Polysaccharides I structure, characterisation and use*. *Advances in polymer science*. Berlin; New York: Springer (pp. x, 281 p.).
- Heinze, T., Koschella, A., & Ebringerová, A. (2003). *Chemical functionalization of xylan: A short review*. *Hemicelluloses: Science and technology*, Vol. 864. American Chemical Society 312–325.
- Hitchcock, A. M., Costello, C. E., & Zaia, J. (2006). Glycoform quantification of chondroitin/dermatan sulfate using a liquid chromatography-tandem mass spectrometry platform. *Biochemistry*, 45(7), 2350–2361.
- Hrynyk, M., Martins-Green, M., Barron, A. E., & Neufeld, R. J. (2012). Alginate-PEG sponge architecture and role in the design of insulin release dressings. *Biomacromolecules*, 13(5), 1478–1485.
- Hu, W. W., & Tsou, S. L. (2014). The effect of alginate on DNA delivery from layer-by-layer assembled films. *Carbohydrate Polymers*, 101, 240–248.
- Isiklan, N., & Kucukbalci, G. (2012). Microwave-induced synthesis of alginate-graft-poly(*N*-isopropylacrylamide) and drug release properties of dual pH- and temperature-responsive beads. *European Journal of Pharmaceutics and Biopharmaceutics*, 82(2), 316–331.
- Isogai, A., Saito, T., & Fukuzumi, H. (2011). TEMPO-oxidized cellulose nanofibers. *Nanoscale*, 3(1), 71–85.
- Ito, T., Yoshida, C., & Murakami, Y. (2013). Design of novel sheet-shaped chitosan hydrogel for wound healing: A hybrid biomaterial consisting of both PEG-grafted chitosan and crosslinkable polymeric micelles acting as drug containers. *Materials Science and Engineering C: Materials for Biological Applications*, 33(7), 3697–3703.
- Jackson, J. K., Letchford, K., Wasserman, B. Z., Ye, L., Hamad, W. Y., & Burt, H. M. (2011). The use of nanocrystalline cellulose for the binding and controlled release of drugs. *International Journal of Nanomedicine*, 6, 321–330.
- Jain, A., Gulbake, A., Shilpi, S., Jain, A., Hurkat, P., & Jain, S. K. (2013). A new horizon in modifications of chitosan: Syntheses and applications. *Critical Reviews in Therapeutic Drug Carrier Systems*, 30(2), 91–181.
- Jain, A. K., Soderlind, E., Viriden, A., Schug, B., Abrahamsson, B., Knopke, C., Tajarobi, F., Blume, H., Anschutz, M., Welinder, A., Richardson, S., Nagel, S., Abrahamsen-Alami, S., & Weitschies, W. (2014). The influence of hydroxypropyl methylcellulose (HPMC) molecular weight, concentration and effect of food on in vivo erosion behavior of HPMC matrix tablets. *Journal of Controlled Release*.
- Jayakumar, R., Chennazhi, K. P., Srinivasan, S., Nair, S. V., Furuike, T., & Tamura, H. (2011). Chitin scaffolds in tissue engineering. *International Journal of Molecular Sciences*, 12(3), 1876–1887.
- Jelinkova, M., Briestensky, J., Santar, I., & Rihova, B. (2002). In vitro and in vivo immunomodulatory effects of microdispersed oxidized cellulose. *International Immunopharmacology*, 2(10), 1429–1441.
- Jeon, O., Samorezov, J. E., & Alsberg, E. (2014). Single and dual crosslinked oxidized methacrylated alginate/PEG hydrogels for bioadhesive applications. *Acta Biomaterialia*, 10(1), 47–55.
- Ji, A. M., Su, D., Che, O., Li, W. S., Sun, L., Zhang, Z. Y., Yang, B., & Xu, F. (2009). Functional gene silencing mediated by chitosan/siRNA nanocomplexes. *Nanotechnology*, 20(40), 405103.
- Jia, S., Li, F., Liu, Y., Ren, H., Gong, G., Wang, Y., & Wu, S. (2013). Effects of extraction methods on the antioxidant activities of polysaccharides from *Agaricus blazei* Murrill. *International Journal of Biological Macromolecules*, 62, 66–69.
- Jiao, G., Yu, G., Zhang, J., & Ewart, H. S. (2011). Chemical structures and bioactivities of sulfated polysaccharides from marine algae. *Marine Drugs*, 9(2), 196–223.
- Jin, M., Huang, Q., Zhao, K., & Shang, P. (2013). Biological activities and potential health benefit effects of polysaccharides isolated from *Lycium barbarum* L. *International Journal of Biological Macromolecules*, 54, 16–23.
- Kalia, S., Kaith, B. S., & Inderjeet, K. (2011). *Cellulose fibers bio- and nano-polymer composites; green chemistry and technology* (p. 1) Berlin; Heidelberg; New York: Springer (online resource (xix, 737 p.)).
- Kamerling, J. P., & Boons, G.-J. (2007). *Comprehensive glycoscience: From chemistry to systems biology*. Amsterdam; Boston: Elsevier.
- Kang, S.-M., Kim, K.-N., Lee, S.-H., Ahn, G., Cha, S.-H., Kim, A.-D., Yang, X.-D., Kang, M.-C., & Jeon, Y.-J. (2011). Anti-inflammatory activity of polysaccharide purified from AMG-assistant extract of *Ecklonia cava* in LPS-stimulated RAW 264.7 macrophages. *Carbohydrate Polymers*, 85(1), 80–85.
- Katas, H., & Alpar, H. O. (2006). Development and characterisation of chitosan nanoparticles for siRNA delivery. *Journal of Controlled Release*, 115(2), 216–225.
- Kaur, I., Kumar, R., & Sharma, N. (2010). A comparative study on the graft copolymerization of acrylic acid onto rayon fibre by a

- ceric ion redox system and a gamma-radiation method. *Carbohydrate Research*, 345(15), 2164–2173.
- Ke, M., Zhang, X.-J., Han, Z.-H., Yu, H.-Y., Lin, Y., Zhang, W.-G., Sun, F.-H., & Wang, T.-J. (2011). Extraction, purification of *Lycium barbarum* polysaccharides and bioactivity of purified fraction. *Carbohydrate Polymers*, 86(1), 136–141.
- Kean, T., Roth, S., & Thanou, M. (2005). Trimethylated chitosans as non-viral gene delivery vectors: Cytotoxicity and transfection efficiency. *Journal of Controlled Release*, 103(3), 643–653.
- Kendall, C. W. C., Esfahani, A., & Jenkins, D. J. A. (2010). The link between dietary fibre and human health. *Food Hydrocolloids*, 24(1), 42–48.
- Khan, F., & Ahmad, S. R. (2013). Polysaccharides and their derivatives for versatile tissue engineering application. *Macromolecular Bioscience*, 13(4), 395–421.
- Khor, E., & Lim, L. Y. (2003). Implantable applications of chitin and chitosan. *Biomaterials*, 24(13), 2339–2349.
- Kim, I. H., Park, J. H., Cheong, I. W., & Kim, J. H. (2003). Swelling and drug release behavior of tablets coated with aqueous hydroxypropyl methylcellulose phthalate (HPMCP) nanoparticles. *Journal of Controlled Release*, 89(2), 225–233.
- Kim, J. H., Lee, S. B., Kim, S. J., & Lee, Y. M. (2002). Rapid temperature/pH response of porous alginate-*g*-poly(*N*-isopropylacrylamide) hydrogels. *Polymer*, 43(26), 7549–7558.
- Kim, S.-K. (2013). Chitin and chitosan derivatives: *Advances in drug discovery and developments*.
- Kim, S. K., & Li, Y. X. (2011). Medicinal benefits of sulfated polysaccharides from sea vegetables. *Advances in Food and Nutrition Research*, 64, 391–402.
- Kim, W. S., Mooney, D. J., Arany, P. R., Lee, K., Huebsch, N., & Kim, J. (2012). Adipose tissue engineering using injectable, oxidized alginate hydrogels. *Tissue Engineering Part A*, 18(7–8), 737–743.
- Kisonen, V., Eklund, P., Auer, M., Sjöholm, R., Pranovich, A., Hemming, J., Sundberg, A., Aseyev, V., & Willför, S. (2012). Hydrophobication and characterisation of O-acetyl-galactoglucomannan for papermaking and barrier applications. *Carbohydrate Research*, 352(0), 151–158.
- Kisonen, V., Xu, C., Eklund, P., Lindqvist, H., Sundberg, A., Pranovich, A., Sinkkonen, J., Vilaplana, F., & Willför, S. (2014). Cationised O-acetyl galactoglucomannans: Synthesis and characterisation. *Carbohydrate Polymers*, 99(0), 755–764.
- Kochumalayil, J. J., Zhou, Q., Kasai, W., & Berglund, L. A. (2013). Regioselective modification of a xyloglucan hemicellulose for high-performance biopolymer barrier films. *Carbohydrate Polymers*, 93(2), 466–472.
- Kolakovic, R., Peltonen, L., Laukkanen, A., Hirvonen, J., & Laaksonen, T. (2012). Nanofibrillar cellulose films for controlled drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics*, 82(2), 308–315.
- Kondo, S., Niiyama, H., Yu, A., & Kuroyanagi, Y. (2011). Evaluation of a wound dressing composed of hyaluronic acid and collagen sponge containing epidermal growth factor in diabetic mice. *Journal of Biomaterials Science Polymer Edition*.
- Kong, J. H., Oh, E. J., Chae, S. Y., Lee, K. C., & Hahn, S. K. (2010). Long acting hyaluronate—Exendin 4 conjugate for the treatment of type 2 diabetes. *Biomaterials*, 31(14), 4121–4128.
- Koschella, A., Fenn, D., Illy, N., & Heinze, T. (2006). Regioselectively functionalized cellulose derivatives: A mini review. *Macromolecular Symposia*, 244(1), 59–73.
- Kumar, M. N. V. R., Muzzarelli, R. A. A., Muzzarelli, C., Sashiwa, H., & Domb, A. J. (2004). Chitosan chemistry and pharmaceutical perspectives. *Chemical Reviews*, 104(12), 6017–6084.
- Kumar, P., Choonara, Y. E., Toit, L. C., Modi, G., Naidoo, D., & Pillay, V. (2012). Novel high-viscosity polyacrylamidated chitosan for neural tissue engineering: Fabrication of anisotropic neurodurable scaffold via molecular disposition of persulfate-mediated polymer slicing and complexation. *International Journal of Molecular Sciences*, 13(11), 13966–13984.
- Kumar, V., & Yang, T. (2002). HNO₃/H₃PO₄-NANO₂ mediated oxidation of cellulose—Preparation and characterization of bioabsorbable oxidized celluloses in high yields and with different levels of oxidation. *Carbohydrate Polymers*, 48(4), 403–412.
- Kuzmenko, V., Hägg, D., Toriz, G., & Gatenholm, P. In situ forming spruce xylan-based hydrogel for cell immobilization. *Carbohydrate Polymers* (0).
- Kwok, J. C., Warren, P., & Fawcett, J. W. (2012). Chondroitin sulfate: A key molecule in the brain matrix. *International Journal of Biochemistry & Cell Biology*, 44(4), 582–586.
- Kyzas, G. Z., Lazaridis, N. K., & Bikiaris, D. N. (2013). Optimization of chitosan and beta-cyclodextrin molecularly imprinted polymer synthesis for dye adsorption. *Carbohydrate Polymers*, 91(1), 198–208.
- Lacin, N. T. (2014). Development of biodegradable antibacterial cellulose based hydrogel membranes for wound healing. *International Journal of Biological Macromolecules*, 67, 22–27.
- Laine, P., Lampi, A.-M., Peura, M., Kansikas, J., Mikkonen, K., Willför, S., Tenkanen, M., & Jouppila, K. (2010). Comparison of microencapsulation properties of spruce galactoglucomannans and arabic gum using a model hydrophobic core compound. *Journal of Agricultural and Food Chemistry*, 58(2), 981–989.
- Laurienzo, P., Malinconico, M., Motta, A., & Vicinanza, A. (2005). Synthesis and characterization of a novel alginate–poly(ethylene glycol) graft copolymer. *Carbohydrate Polymers*, 62(3), 274–282.
- Lazaridou, A., Chornick, T., Biliaderis, C. G., & Izydorczyk, M. S. (2008). Composition and molecular structure of polysaccharides released from barley endosperm cell walls by sequential extraction with water, malt enzymes, and alkali. *Journal of Cereal Science*, 48(2), 304–318.
- Le Normand, M., Melida, H., Holmbom, B., Michaelsen, T. E., Inggerdingen, M., Bulone, V., Paulsen, B. S., & Ek, M. (2014). Hot-water extracts from the inner bark of Norway spruce with immunomodulating activities. *Carbohydrate Polymers*, 101, 699–704.
- Leppänen, A.-S., Xu, C., Eklund, P., Lucenius, J., Österberg, M., & Willför, S. (2013). Targeted functionalization of spruce O-acetyl galactoglucomannans—2,2,6,6-Tetramethylpiperidin-1-oxyl-oxidation and carbodiimide-mediated amidation. *Journal of Applied Polymer Science*, 130(5), 3122–3129.
- Leppänen, A.-S., Xu, C., Parikka, K., Eklund, P., Sjöholm, R., Brumer, H., Tenkanen, M., & Willför, S. (2014). Targeted allylation and propargylation of galactose-containing polysaccharides in water. *Carbohydrate Polymers*, 100, 46–54.
- Li, H., Mao, W., Hou, Y., Gao, Y., Qi, X., Zhao, C., Chen, Y., Chen, Y., Li, N., & Wang, C. (2012a). Preparation, structure and anticoagulant activity of a low molecular weight fraction produced by mild acid hydrolysis of sulfated rhamnan from *Monostroma latissimum*. *Bioresource Technology*, 114, 414–418.
- Li, J., & Mei, X. (2006). Applications of cellulose and cellulose derivatives in immediate release solid dosage. *Polysaccharides for drug delivery and pharmaceutical applications*, Vol. 934. American Chemical Society 19–55.
- Li, J., Zhong, Y., Li, H., Zhang, N., Ma, W., Cheng, G., Liu, F., Liu, F., & Xu, J. (2011). Enhancement of Astragalus polysaccharide on the immune responses in pigs inoculated with foot-and-mouth disease virus vaccine. *International Journal of Biological Macromolecules*, 49(3), 362–368.
- Li, T., & Peng, T. (2013). Traditional Chinese herbal medicine as a source of molecules with antiviral activity. *Antiviral Research*, 97(1), 1–9.
- Li, X., Chen, S., Zhang, B., Li, M., Diao, K., Zhang, Z., Li, J., Xu, Y., Wang, X., & Chen, H. (2012b). In situ injectable nano-composite

- hydrogel composed of curcumin, N,O-carboxymethyl chitosan and oxidized alginate for wound healing application. *International Journal of Pharmaceutics*, 437(1–2), 110–119.
- Liakos, I., Rizzello, L., Bayer, I. S., Pompa, P. P., Cingolani, R., & Athanassiou, A. (2013). Controlled antiseptic release by alginate polymer films and beads. *Carbohydrate Polymers*, 92(1), 176–183.
- Liakos, I., Rizzello, L., Scurr, D. J., Pompa, P. P., Bayer, I. S., & Athanassiou, A. (2013). All-natural composite wound dressing films of essential oils encapsulated in sodium alginate with antimicrobial properties. *International Journal of Pharmaceutics*.
- Lindblad, M. S., Dahlman, O., Sjöberg, J., & Albertsson, A.-C. (2009). Modified galactoglucomannans from forestry waste-water for films and hydrogels. *Polysaccharide materials: Performance by design*, Vol. 1017. American Chemical Society 185–198.
- Lindblad, M. S., Sjöberg, J., Albertsson, A.-C., & Hartman, J. (2007). Hydrogels from polysaccharides for biomedical applications. *Materials, chemicals, and energy from forest biomass*, Vol. 954. American Chemical Society 153–167.
- Linhardt, R. J. (2003). Heparin: Structure and activity. *Journal of Medicinal Chemistry*, 46(13), 2551–2564.
- Liu, L., Fishman, M. L., Kost, J., & Hicks, K. B. (2003). Pectin-based systems for colon-specific drug delivery via oral route. *Biomaterials*, 24(19), 3333–3343.
- Liu, W., Liu, J., Liu, W., Li, T., & Liu, C. (2013). Improved physical and in vitro digestion stability of a polyelectrolyte delivery system based on layer-by-layer self-assembly alginate-chitosan-coated nanoliposomes. *Journal of Agricultural and Food Chemistry*, 61(17), 4133–4144.
- Liu, Z., Jiao, Y., Wang, Y., Zhou, C., & Zhang, Z. (2008). Polysaccharides-based nanoparticles as drug delivery systems. *Advanced Drug Delivery Reviews*, 60(15), 1650–1662.
- Logesh, A. R., Thillaimaharani, K. A., Sharmila, K., Kalaiselvam, M., & Raffi, S. M. (2012). Production of chitosan from endolichenic fungi isolated from mangrove environment and its antagonistic activity. *Asian Pacific Journal of Tropical Biomedicine*, 2(2), 140–143.
- Lu, B., Xu, X. D., Zhang, X. Z., Cheng, S. X., & Zhuo, R. X. (2008). Low molecular weight polyethylenimine grafted N-maleated chitosan for gene delivery: Properties and in vitro transfection studies. *Biomacromolecules*, 9(10), 2594–2600.
- Lu, H. F., Lim, S. X., Leong, M. F., Narayanan, K., Toh, R. P., Gao, S., & Wan, A. C. (2012). Efficient neuronal differentiation and maturation of human pluripotent stem cells encapsulated in 3D microfibrillar scaffolds. *Biomaterials*, 33(36), 9179–9187.
- Lu, H. F., Narayanan, K., Lim, S. X., Gao, S., Leong, M. F., & Wan, A. C. (2012). A 3D microfibrillar scaffold for long-term human pluripotent stem cell self-renewal under chemically defined conditions. *Biomaterials*, 33(8), 2419–2430.
- Lunn, J., & Buttriss, J. L. (2007). Carbohydrates and dietary fibre. *Nutrition Bulletin*, 32(1), 21–64.
- Luo, Y., & Wang, Q. (2013). Recent development of chitosan-based polyelectrolyte complexes with natural polysaccharides for drug delivery. *International Journal of Biological Macromolecules*(0).
- Lv, L., Cheng, Y., Zheng, T., Li, X., & Zhai, R. (2014). Purification, antioxidant activity and antigenicity of polysaccharides from *Polygonum multiflorum* Thunb. *Carbohydrate Polymers*, 99, 765–773.
- Mäki-Arvela, P., Salmi, T., Holmbom, B., Willför, S., & Murzin, D. Y. (2011). Synthesis of sugars by hydrolysis of hemicelluloses—A review. *Chemical Reviews*, 111(9), 5638–5666.
- Maeda, M., Uehara, T., Harada, N., Sekiguchi, M., & Hiraoka, A. (1991). Heparinoid-active sulphated polysaccharides from *Monostroma nitidum* and their distribution in the chlorophyta. *Phytochemistry*, 30(11), 3611–3614.
- Maleki, A., Kjoniksen, A. L., & Nystrom, B. (2007). Characterization of the chemical degradation of hyaluronic acid during chemical gelation in the presence of different cross-linker agents. *Carbohydrate Research*, 342(18), 2776–2792.
- Mao, S., Sun, W., & Kissel, T. (2010). Chitosan-based formulations for delivery of DNA and siRNA. *Advanced Drug Delivery Reviews*, 62(1), 12–27.
- Mao, W., Li, H., Li, Y., Zhang, H., Qi, X., Sun, H., Chen, Y., & Guo, S. (2009). Chemical characteristic and anticoagulant activity of the sulfated polysaccharide isolated from *Monostroma latissimum* (Chlorophyta). *International Journal of Biological Macromolecules*, 44(1), 70–74.
- Marchessault, R. H., Ravenelle, F., & Zhu, X. X. (2006). *Polysaccharides for drug delivery and pharmaceutical applications*. Washington, DC: American Chemical Society: Distributed by Oxford University Press.
- Marques, A., Dhont, J., Sorgeloos, P., & Bossier, P. (2006). Immunostimulatory nature of beta-glucans and baker's yeast in gnotobiotic *Artemia* challenge tests. *Fish and Shellfish Immunology*, 20(5), 682–692.
- Martinichen-Herrero, J. C., Carbonero, E. R., Sassaki, G. L., Gorin, P. A., & Iacomini, M. (2005). Anticoagulant and antithrombotic activities of a chemically sulfated galactoglucomannan obtained from the lichen *Cladonia ibitipocae*. *International Journal of Biological Macromolecules*, 35(1–2), 97–102.
- Maslen, S. L., Goubet, F., Adam, A., Dupree, P., & Stephens, E. (2007). Structure elucidation of arabinoxylan isomers by normal phase HPLC–MALDI–TOF/TOF–MS/MS. *Carbohydrate Research*, 342(5), 724–735.
- Matricardi, P., Di Meo, C., Coviello, T., Hennink, W. E., & Alhaique, F. (2013). Interpenetrating polymer networks polysaccharide hydrogels for drug delivery and tissue engineering. *Advanced Drug Delivery Reviews*, 65(9), 1172–1187.
- Matsumoto, Y., & Kuroyanagi, Y. (2010). Development of a wound dressing composed of hyaluronic acid sponge containing arginine and epidermal growth factor. *Journal of Biomaterials Science Polymer Edition*, 21(6), 715–726.
- Mazumder, M. A., Burke, N. A., Shen, F., Potter, M. A., & Stover, H. D. (2009). Core-cross-linked alginate microcapsules for cell encapsulation. *Biomacromolecules*, 10(6), 1365–1373.
- Mazumder, M. A., Shen, F., Burke, N. A., Potter, M. A., & Stover, H. D. (2008). Self-cross-linking polyelectrolyte complexes for therapeutic cell encapsulation. *Biomacromolecules*, 9(9), 2292–2300.
- Miranda, E. S., Silva, T. H., Reis, R. L., & Mano, J. F. (2011). Nanostructured natural-based polyelectrolyte multilayers to agglomerate chitosan particles into scaffolds for tissue engineering. *Tissue Engineering Part A*, 17(21–22), 2663–2674.
- Mischnick, P. (2012). Mass spectrometric characterization of oligo- and polysaccharides and their derivatives. In M. Hakkarainen (Ed.), *Mass spectrometry of polymers—New techniques*, Vol. 248 (pp. 105–174). Berlin Heidelberg: Springer.
- Mizrahy, S., & Peer, D. (2012). Polysaccharides as building blocks for nanotherapeutics. *Chemical Society Reviews*, 41(7), 2623–2640.
- Mohd Amin, M. C., Ahmad, N., Pandey, M., & Jue Xin, C. (2013). Stimuli-responsive bacterial cellulose-g-poly(acrylic acid-co-acrylamide) hydrogels for oral controlled release drug delivery. *Drug Development and Industrial Pharmacy*.
- Monier, M., & El-Mekabaty, A. (2013). Preparation of molecularly imprinted resin based on chitosan for chiral recognition of S-mandelic acid. *International Journal of Biological Macromolecules*, 55, 207–213.
- Morris, G., Kok, S., Harding, S., & Adams, G. (2010). Polysaccharide drug delivery systems based on pectin and chitosan. *Biotechnology & Genetic Engineering Reviews*, 27, 257–284.
- Mourya, V. K., & Inamdar, N. N. (2008). Chitosan-modifications and applications: Opportunities galore. *Reactive and Functional Polymers*, 68(6), 1013–1051.
- Mudgil, D., & Barak, S. (2013). Composition, properties and health benefits of indigestible carbohydrate polymers as dietary fiber: A review. *International Journal of Biological Macromolecules*, 61, 1–6.

- Munarin, F., Tanzi, M. C., & Petrini, P. (2012). Advances in biomedical applications of pectin gels. *International Journal of Biological Macromolecules*, 51(4), 681–689.
- Muzzarelli, R. A. A., & Muzzarelli, C. (2005). Chitosan chemistry: Relevance to the biomedical sciences. In T. Heinze (Ed.), *Polysaccharides I*, Vol. 186 (pp. 151–209). Berlin Heidelberg: Springer.
- Nakamatsu, J., Torres, F. G., Troncoso, O. P., Min-Lin, Y., & Boccaccini, A. R. (2006). Processing and characterization of porous structures from chitosan and starch for tissue engineering scaffolds. *Biomacromolecules*, 7(12), 3345–3355.
- Nemtsev, S. V., Gamzade, A. I., Rogozhin, S. V., Bykova, V. M., & Bykov, V. P. (2002). Deacetylation of chitin under homogeneous conditions. *Applied Biochemistry and Microbiology*, 38(6), 521–526.
- Ngo, D. H., & Kim, S. K. (2013). Sulfated polysaccharides as bioactive agents from marine algae. *International Journal of Biological Macromolecules*, 62, 70–75.
- Novotna, K., Havelka, P., Sopuch, T., Kolarova, K., Vosmanska, V., Lisa, V., Svorcik, V., & Bacakova, L. (2013). Cellulose-based materials as scaffolds for tissue engineering. *Cellulose*, 20(5), 2263–2278.
- Oh, E. J., Park, K., Kim, K. S., Kim, J., Yang, J. A., Kong, J. H., Lee, M. Y., Hoffman, A. S., & Hahn, S. K. (2010). Target specific and long-acting delivery of protein, peptide, and nucleotide therapeutics using hyaluronic acid derivatives. *Journal of Controlled Release*, 141(1), 2–12.
- Olafsdottir, E. S., & Ingólfssdottir, K. (2001). Polysaccharides from lichens: Structural characteristics and biological activity. *Planta Medica*, 67(3), 199–208.
- Oliveira, J. T., & Reis, R. L. (2011). Polysaccharide-based materials for cartilage tissue engineering applications. *Journal of Tissue Engineering and Regenerative Medicine*, 5(6), 421–436.
- Omarsdottir, S., Freysdottir, J., & Olafsdottir, E. S. (2007). Immunomodulating polysaccharides from the lichen *Thamnolia vermicularis* var. *subuliformis*. *Phytomedicine*, 14(2–3), 179–184.
- Omarsdottir, S., Olafsdottir, E. S., & Freysdottir, J. (2006). Immunomodulating effects of lichen-derived polysaccharides on monocyte-derived dendritic cells. *International Immunopharmacology*, 6(11), 1642–1650.
- Orelma, H., Filpponen, I., Johansson, L. S., Österberg, M., Rojas, O. J., & Laine, J. (2012a). Surface functionalized nanofibrillar cellulose (NFC) film as a platform for immunoassays and diagnostics. *Biointerphases*, 7(1–4), 61.
- Orelma, H., Johansson, L. S., Filpponen, I., Rojas, O. J., & Laine, J. (2012b). Generic method for attaching biomolecules via avidin-biotin complexes immobilized on films of regenerated and nanofibrillar cellulose. *Biomacromolecules*, 13(9), 2802–2810.
- Pérez, S., & Bertoft, E. (2010). The molecular structures of starch components and their contribution to the architecture of starch granules: A comprehensive review. *Starch-Stärke*, 62(8), 389–420.
- Pérez, S., & Samain, D. (2010). Structure and engineering of celluloses. In H. Derek (Ed.), *Advances in carbohydrate chemistry and biochemistry*, Vol 64 (pp. 25–116). Academic Press: Academic Press, 2010.
- Pachua, L., & Mazumder, B. (2013). Colonic drug delivery systems based on natural polysaccharides and their evaluation. *Mini Reviews in Medicinal Chemistry*, 13(13), 1982–1991.
- Parikka, K., Leppänen, A.-S., Xu, C., Pitkänen, L., Eronen, P., Österberg, M., Brumer, H., Willför, S., & Tenkanen, M. (2012). Functional and anionic cellulose-interacting polymers by selective chemo-enzymatic carboxylation of galactose-containing polysaccharides. *Biomacromolecules*, 13(8), 2418–2428.
- Parikka, K., Leppänen, A.-S., Pitkänen, L., Reunanen, M., Willför, S., & Tenkanen, M. (2009). Oxidation of polysaccharides by galactose oxidase. *Journal of Agricultural and Food Chemistry*, 58(1), 262–271.
- Pawar, S. N., & Edgar, K. J. (2012). Alginate derivatization: A review of chemistry, properties and applications. *Biomaterials*, 33(11), 3279–3305.
- Pawar, S. N., & Edgar, K. J. (2013). Alginate esters via chemoselective carboxyl group modification. *Carbohydrate Polymers*, 98(2), 1288–1296.
- Peng, X.-W., Ren, J.-L., Zhong, L.-X., Peng, F., & Sun, R.-C. (2011). Xylan-rich hemicelluloses-graft-acrylic acid ionic hydrogels with rapid responses to pH, salt, and organic solvents. *Journal of Agricultural and Food Chemistry*, 59(15), 8208–8215.
- Petzold-Welcke, K., Schwikal, K., Daus, S., & Heinze, T. (2014). Xylan derivatives and their application potential—Mini-review of own results. *Carbohydrate Polymers*, 100(0), 80–88.
- Pigorsch, E. (2009). Spectroscopic characterisation of cationic quaternary ammonium starches. *Starch-Stärke*, 61(3–4), 129–138.
- Pillai, C. K. S., Paul, W., & Sharma, C. P. (2009). Chitin and chitosan polymers: Chemistry, solubility and fiber formation. *Progress in Polymer Science*, 34(7), 641–678.
- Pitarresi, G., Calabrese, R., Palumbo, F. S., Licciardi, M., & Giammona, G. (2009). Polysaccharide/polyaminoacid composite scaffolds for modified DNA release. *International Journal of Pharmaceutics*, 382(1–2), 7–14.
- Plackett, D. V., Letchford, K., JacksonJohn, K., & Burt, H. M. (2014). A review of nanocellulose as a novel vehicle for drug delivery. *Nordic Pulp & Paper Research Journal*, 29(1), 105–118.
- Pohjanlehto, H., Setälä, H., Kammiovirta, K., & Harlin, A. (2011). The use of N,N'-diallyldiamides as cross-linkers in xylan derivatives-based hydrogels. *Carbohydrate Research*, 346(17), 2736–2745.
- Ponce, N. M., Pujol, C. A., Damonte, E. B., Flores, M. L., & Stortz, C. A. (2003). Fucoidans from the brown seaweed *Adenocystis utricularis*: Extraction methods, antiviral activity and structural studies. *Carbohydrate Research*, 338(2), 153–165.
- Pool-Zobel, B. L. (2005). Inulin-type fructans and reduction in colon cancer risk: Review of experimental and human data. *British Journal of Nutrition*, 93(Suppl 1), S73–90.
- Prestwich, G. D. (2007). Simplifying the extracellular matrix for 3-D cell culture and tissue engineering: A pragmatic approach. *Journal of Cellular Biochemistry*, 101(6), 1370–1383.
- Prestwich, G. D. (2011). Hyaluronic acid-based clinical biomaterials derived for cell and molecule delivery in regenerative medicine. *Journal of Controlled Release*, 155(2), 193–199.
- Prestwich, G. D., & Kuo, J. W. (2008). Chemically-modified HA for therapy and regenerative medicine. *Current Pharmaceutical Biotechnology*, 9(4), 242–245.
- Puri, M., Sharma, D., & Barrow, C. J. (2012). Enzyme-assisted extraction of bioactives from plants. *Trends in Biotechnology*, 30(1), 37–44.
- Ragelle, H., Vandermeulen, G., & Preat, V. (2013). Chitosan-based siRNA delivery systems. *Journal of Controlled Release*, 172(1), 207–218.
- Rajangam, K., Behanna, H. A., Hui, M. J., Han, X., Hulvat, J. F., Lomasney, J. W., & Stupp, S. I. (2006). Heparin binding nanostructures to promote growth of blood vessels. *Nano Letters*, 6(9), 2086–2090.
- Rattan, S., Maitra, J., Misra, B. N., & Kaur, I. (2008). Radiation induced graft copolymerization of vinyl monomers and their binary mixture onto rayon fibre. *Journal of Applied Polymer Science*, 108(5), 3104–3113.
- Reddy, K., Mohan, G. K., Satla, S., & Gaikwad, S. (2011). Natural polysaccharides: Versatile excipients for controlled drug delivery systems. *Asian Journal of Pharmaceutical Sciences*, 6(6), 275–286.

- Rehm, B. (2009). *Alginates biology and applications*. Microbiology monographs, vol 13. Berlin; Heidelberg: Springer-Verlag.
- Ridley, B. L., O'Neill, M. A., & Mohnen, D. (2001). Pectins: Structure, biosynthesis, and oligogalacturonide-related signaling. *Phytochemistry*, 57(6), 929–967.
- Rinaudo, M. (2008). Main properties and current applications of some polysaccharides as biomaterials. *Polymer International*, 57(3), 397–430.
- Roberts, J. R., Ritter, D. W., & McShane, M. J. (2013). A design full of holes: Functional nanofilm-coated microdomains in alginate hydrogels. *Journal of Materials Chemistry B: Materials for Biology and Medicine*, 107(25), 3195–3201.
- Russo, F., Linsalata, M., Clemente, C., Chiloire, M., Orlando, A., Marconi, E., Chimienti, G., & Riezzo, G. (2012). Inulin-enriched pasta improves intestinal permeability and modifies the circulating levels of zonulin and glucagon-like peptide 2 in healthy young volunteers. *Nutrition Research*, 32(12), 940–946.
- Rutkaite, R., Bendoraitiene, J., Klimaviciute, R., & Zemaitaitis, A. (2012). Cationic starch nanoparticles based on polyelectrolyte complexes. *International Journal of Biological Macromolecules*, 50(3), 687–693.
- Sakiyama-Elbert, S. E. (2014). Incorporation of heparin into biomaterials. *Acta Biomaterialia*, 10(4), 1581–1587.
- Sandra, K. (2009). Polysaccharides in oral drug delivery? *Recent applications and future perspectives*. Polysaccharide materials: Performance by design, Vol. 1017. American Chemical Society 13–30.
- Santo, V. E., Gomes, M. E., Mano, J. F., & Reis, R. L. (2012). Chitosan-chondroitin sulphate nanoparticles for controlled delivery of platelet lysates in bone regenerative medicine. *Journal of Tissue Engineering and Regenerative Medicine*, 6(Suppl 3), s47–59.
- Schanté, C. E., Zuber, G., Herlin, C., & Vandamme, T. F. (2011). Chemical modifications of hyaluronic acid for the synthesis of derivatives for a broad range of biomedical applications. *Carbohydrate Polymers*, 85(3), 469–489.
- Schedin-Weiss, S., Richard, B., Hjelm, R., & Olson, S. T. (2008). Antiangiogenic forms of antithrombin specifically bind to the anticoagulant heparin sequence. *Biochemistry*, 47(51), 13610–13619.
- Schepetkin, I. A., & Quinn, M. T. (2006). Botanical polysaccharides: Macrophage immunomodulation and therapeutic potential. *International Immunopharmacology*, 6(3), 317–333.
- Schneider, A., Richert, L., Francius, G., Voegel, J. C., & Picart, C. (2007). Elasticity, biodegradability and cell adhesive properties of chitosan/hyaluronan multilayer films. *Biomedical Materials*, 2(1), S45–51.
- Schuchman, E. H., Ge, Y., Lai, A., Borisov, Y., Faillace, M., Eliyahu, E., He, X., Iatridis, J., Vlassara, H., Striker, G., & Simonaro, C. M. (2013). Pentosan polysulfate: A novel therapy for the mucopolysaccharidoses. *PLoS One*, 8(1), e54459.
- Sehaqui, H., Zhou, Q., & Berglund, L. A. (2011). High-porosity aerogels of high specific surface area prepared from nanofibrillated cellulose (NFC). *Composites Science and Technology*, 71(13), 1593–1599.
- Shelke, N. B., James, R., Laurencin, C. T., & Kumbar, S. G. (2014). Polysaccharide biomaterials for drug delivery and regenerative engineering. *Polymers for Advanced Technologies*, 25(5), 448–460.
- Shimotoyodome, A., Suzuki, J., Kumamoto, Y., Hase, T., & Isogai, A. (2011). Regulation of postprandial blood metabolic variables by TEMPO-oxidized cellulose nanofibers. *Biomacromolecules*, 12(10), 3812–3818.
- Silbert, J. E., & Sugumaran, G. (2002). Biosynthesis of chondroitin/dermatan sulfate. *IUBMB Life*, 54(4), 177–186.
- Silva, J. M., Duarte, A. R., Custodio, C. A., Sher, P., Neto, A. I., Pinho, A. C., Fonseca, J., Reis, R. L., & Mano, J. F. (2013a). Nanostructured hollow tubes based on chitosan and alginate multilayers. *Advanced Healthcare Materials*
- Silva, J. M., Georgi, N., Costa, R., Sher, P., Reis, R. L., Van Blitterswijk, C. A., Karperien, M., & Mano, J. F. (2013b). Nanostructured 3D constructs based on chitosan and chondroitin sulphate multilayers for cartilage tissue engineering. *PLoS One*, 8(2), e55451.
- Singh, R., & Singh, D. (2012). Radiation synthesis of PVP/alginate hydrogel containing nanosilver as wound dressing. *Journal of Materials Science: Materials in Medicine*, 23(11), 2649–2658.
- Song, T., Pranovich, A., & Holmbom, B. (2013). Separation of polymeric galactoglucomannans from hot-water extract of spruce wood. *Bioresource Technology*, 130, 198–203.
- Spiller, K. L., Maher, S. A., & Lowman, A. M. (2011). Hydrogels for the repair of articular cartilage defects. *Tissue Engineering Part B: Reviews*, 17(4), 281–299.
- Spizzirri, U. G., Parisi, O. I., Iemma, F., Cirillo, G., Puoci, F., Curcio, M., & Picci, N. (2010). Antioxidant-polysaccharide conjugates for food application by eco-friendly grafting procedure. *Carbohydrate Polymers*, 79(2), 333–340.
- Srivastava, M., & Kapoor, V. P. (2005). Seed galactomannans: An overview. *Chemistry & Biodiversity*, 2(3), 295–317.
- Srivastava, R., & McShane, M. J. (2005). Application of self-assembled ultra-thin film coatings to stabilize macromolecule encapsulation in alginate microspheres. *Journal of Microencapsulation*, 22(4), 397–411.
- Sugahara, K., Mikami, T., Uyama, T., Mizuguchi, S., Nomura, K., & Kitagawa, H. (2003). Recent advances in the structural biology of chondroitin sulfate and dermatan sulfate. *Current Opinion in Structural Biology*, 13(5), 612–620.
- Suh, H. J., Yang, H. S., Ra, K. S., Noh, D. O., Kwon, K. H., Hwang, J. H., & Yu, K. W. (2013). Peyer's patch-mediated intestinal immune system modulating activity of pectic-type polysaccharide from peel of Citrus unshiu. *Food Chemistry*, 138(2–3), 1079–1086.
- Suh, J. K., & Matthew, H. W. (2000). Application of chitosan-based polysaccharide biomaterials in cartilage tissue engineering: A review. *Biomaterials*, 21(24), 2589–2598.
- Tahara, K., Yamamoto, H., Hirashima, N., & Kawashima, Y. (2010). Chitosan-modified poly(D,L-lactide-co-glycolide) nanospheres for improving siRNA delivery and gene-silencing effects. *European Journal of Pharmaceutics and Biopharmaceutics*, 74(3), 421–426.
- Takegawa, Y., Araki, K., Fujitani, N., Furukawa, J., Sugiyama, H., Sakai, H., & Shinohara, Y. (2011). Simultaneous analysis of heparan sulfate, chondroitin/dermatan sulfates, and hyaluronan disaccharides by glycoblotting-assisted sample preparation followed by single-step zwitter-ionic-hydrophilic interaction chromatography. *Analytical Chemistry*, 83(24), 9443–9449.
- Tang, W., Hemm, I., & Bertram, B. (2003a). Recent development of antitumor agents from Chinese herbal medicines. Part II. High molecular compounds(3). *Planta Medica*, 69(3), 193–201.
- Tang, W., Hemm, I., & Bertram, B. (2003b). Recent development of antitumor agents from Chinese herbal medicines; Part I. Low molecular compounds. *Planta Medica*, 69(2), 97–108.
- Tashiro, K., & Kobayashi, M. (1991). Theoretical evaluation of three-dimensional elastic constants of native and regenerated celluloses: Role of hydrogen bonds. *Polymer*, 32(8), 1516–1526.
- Teleman, A., Tenkanen, M., Jacobs, A., & Dahlman, O. (2002). Characterization of O-acetyl-(4-O-methylglucurono)xylan isolated from birch and beech. *Carbohydrate Research*, 337(4), 373–377.
- Tenkanen, M. (2003). Enzymatic tailoring of hemicelluloses. *Hemicelluloses: Science and technology*, Vol. 864. American Chemical Society 292–311.
- Thakur, M., Weng, A., Fuchs, H., Sharma, V., Bhargava, C. S., Chauhan, N. S., Dixit, V. K., & Bhargava, S. (2012). Rasayana properties of Ayurvedic herbs: Are polysaccharides a major contributor. *Carbohydrate Polymers*, 87(1), 3–15.

- Thakur, V. K., Thakur, M. K., & Gupta, R. K. (2013a). Development of functionalized cellulosic biopolymers by graft copolymerization. *International Journal of Biological Macromolecules*, 62, 44–51.
- Thakur, V. K., Thakur, M. K., & Gupta, R. K. (2013b). Rapid synthesis of graft copolymers from natural cellulose fibers. *Carbohydrate Polymers*, 98(1), 820–828.
- Tharanathan, R. N. (2005). Starch—Value addition by modification. *Critical Reviews in Food Science and Nutrition*, 45(5), 371–384.
- Tian, L., Zhao, Y., Guo, C., & Yang, X. (2011). A comparative study on the antioxidant activities of an acidic polysaccharide and various solvent extracts derived from herbal *Houttuynia cordata*. *Carbohydrate Polymers*, 83(2), 537–544.
- Tonnesen, H. H., & Karlsen, J. (2002). Alginate in drug delivery systems. *Drug Development and Industrial Pharmacy*, 28(6), 621–630.
- Trinchero, J., Ponce, N. M., Cordoba, O. L., Flores, M. L., Pampuro, S., Stortz, C. A., Salomon, H., & Turk, G. (2009). Antiretroviral activity of fucoidans extracted from the brown seaweed *Adenocystis utricularis*. *Phytotherapy Research*, 23(5), 707–712.
- Tungland, B. C., & Meyer, D. (2002). Nondigestible oligo- and polysaccharides (dietary fiber): Their physiology and role in human health and food. *Comprehensive Reviews in Food Science and Food Safety*, 1(3), 90–109.
- Tupa, M., Maldonado, L., Vazquez, A., & Foresti, M. L. (2013). Simple organocatalytic route for the synthesis of starch esters. *Carbohydrate Polymers*, 98(1), 349–357.
- Ungewiß, J., Vietzke, J.-P., Rapp, C., Schmidt-Lewerkühne, H., Wittern, K.-P., & Salzer, R. (2005). Quantitative determination of cationic modified polysaccharides on hair using LC-MS and LC-MS-MS. *Analytical and Bioanalytical Chemistry*, 381(7), 1401–1407.
- Valo, H., Arola, S., Laaksonen, P., Torkkeli, M., Peltonen, L., Linder, M. B., Serimaa, R., Kuga, S., Hirvonen, J., & Laaksonen, T. (2013). Drug release from nanoparticles embedded in four different nanofibrillar cellulose aerogels. *European Journal of Pharmaceutical Sciences*, 50(1), 69–77.
- Valo, H., Kovalainen, M., Laaksonen, P., Hakkinen, M., Auriola, S., Peltonen, L., Linder, M., Jarvinen, K., Hirvonen, J., & Laaksonen, T. (2011). Immobilization of protein-coated drug nanoparticles in nanofibrillar cellulose matrices—enhanced stability and release. *Journal of Controlled Release*, 156(3), 390–397.
- Varki, A. (1993). Biological roles of oligosaccharides: All of the theories are correct. *Glycobiology*, 3(2), 97–130.
- Varki, A. (2009). *Essentials of glycobiology*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.
- Venkatesan, J., & Kim, S. K. (2010). Chitosan composites for bone tissue engineering—An overview. *Marine Drugs*, 8(8), 2252–2266.
- Viikari, L., Poutanen, K., Tenkanen, M., & Tolan, J. S. (2002). Hemicellulases. *Encyclopedia of bioprocess technology*. John Wiley & Sons, Inc..
- Viuda-Martos, M., López-Marcos, M. C., Fernández-López, J., Sendra, E., López-Vargas, J. H., & Pérez-Álvarez, J. A. (2010). Role of fiber in cardiovascular diseases: A review. *Comprehensive Reviews in Food Science and Food Safety*, 9(2), 240–258.
- Wan, A. C. A., & Tai, B. C. U. (2013). CHITIN—A promising biomaterial for tissue engineering and stem cell technologies. *Biotechnology Advances*, 31(8), 1776–1785.
- Wang, S., Oommen, O. P., Yan, H., & Varghese, O. P. (2013). Mild and efficient strategy for site-selective aldehyde modification of glycosaminoglycans: Tailoring hydrogels with tunable release of growth factor. *Biomacromolecules*, 14(7), 2427–2432.
- Wang, W., Wang, S. X., & Guan, H. S. (2012). The antiviral activities and mechanisms of marine polysaccharides: An overview. *Marine Drugs*, 10(12), 2795–2816.
- Waterschoot, J., Gomand, S. V., Fierens, E., & Delcour, J. A. (2014). Production, structure, physicochemical and functional properties of maize, cassava, wheat, potato and rice starches. *Starch-Stärke* (n/a-n/a).
- Weng, L. C., Lee, N. J., Yeh, W. T., Ho, L. T., & Pan, W. H. (2012). Lower intake of magnesium and dietary fiber increases the incidence of type 2 diabetes in Taiwanese. *Journal of the Formosan Medical Association*, 111(11), 651–659.
- Whelton, S. P., Hyre, A. D., Pedersen, B., Yi, Y., Whelton, P. K., & He, J. (2005). Effect of dietary fiber intake on blood pressure: A meta-analysis of randomized, controlled clinical trials. *Journal of Hypertension*, 23(3), 475–481.
- Whistler, R. L., & BeMiller, J. N. (1993). *Industrial gums: Polysaccharides and their derivatives*. San Diego: Academic Press.
- Wijesekara, I., Pangestuti, R., & Kim, S.-K. (2011). Biological activities and potential health benefits of sulfated polysaccharides derived from marine algae. *Carbohydrate Polymers*, 84(1), 14–21.
- Willför, S., Sjöholm, R., Laine, C., Roslund, M., Hemming, J., & Holmbom, B. (2003). Characterisation of water-soluble galactoglucomannans from Norway spruce wood and thermomechanical pulp. *Carbohydrate Polymers*, 52(2), 175–187.
- Wolever, T. M., Gibbs, A. L., Brand-Miller, J., Duncan, A. M., Hart, V., Lamarche, B., Tosh, S. M., & Duss, R. (2011). Bioactive oat beta-glucan reduces LDL cholesterol in Caucasians and non-Caucasians. *Nutrition Journal*, 10, 130.
- Wong, T. W. (2011). Alginate graft copolymers and alginate-co-ecipient physical mixture in oral drug delivery. *Journal of Pharmacy and Pharmacology*, 63(12), 1497–1512.
- Wrigstedt, P., Kylli, P., Pitkänen, L., Nousiainen, P., Tenkanen, M., & Sipilä, J. (2010). Synthesis and antioxidant activity of hydroxycinnamic acid xylan esters. *Journal of Agricultural and Food Chemistry*, 58(11), 6937–6943.
- Wu, S., Hu, J., Wei, L., Du, Y., Shi, X., & Zhang, L. (2014). Antioxidant and antimicrobial activity of Maillard reaction products from xylan with chitosan/chitoooligomer/glucosamine hydrochloride/taurine model systems. *Food Chemistry*, 148, 196–203.
- Wu, S. M., & Hochedlinger, K. (2011). Harnessing the potential of induced pluripotent stem cells for regenerative medicine. *Nature Cell Biology*, 13(5), 497–505.
- Wu, W. T., & Chen, H. L. (2011). Konjac glucomannan and inulin systematically modulate antioxidant defense in rats fed a high-fat fiber-free diet. *Journal of Agricultural and Food Chemistry*, 59(17), 9194–9200.
- Wu, Y., He, J., Huang, Y., Wang, F., & Tang, F. (2012). Oxidation of regenerated cellulose with nitrogen dioxide/carbon tetrachloride. *Fibers and Polymers*, 13(5), 576–581.
- Xiao, Z., Tappen, B. R., Ly, M., Zhao, W., Canova, L. P., Guan, H., & Linhardt, R. J. (2011). Heparin mapping using heparin lyases and the generation of a novel low molecular weight heparin. *Journal of Medicinal Chemistry*, 54(2), 603–610.
- Xie, W., & Wang, Y. (2011). Synthesis of high fatty acid starch esters with 1-butyl-3-methylimidazolium chloride as a reaction medium. *Starch-Stärke*, 63(4), 190–197.
- Xu, C., Spadiut, O., Araújo, A. C., Nakhai, A., & Brumer, H. (2012). Chemo-enzymatic assembly of clickable cellulose surfaces via multivalent polysaccharides. *ChemSusChem*, 5(4), 661–665.
- Xu, C. L., Eckerman, C., Smeds, A., Reunanen, M., Eklund, P. C., Sjöholm, R., & Willför, S. (2011). Carboxymethylated spruce galactoglucomannans: Preparation, characterisation, dispersion stability, water-in-oil emulsion stability, and sorption on cellulose surface. *Nordic Pulp & Paper Research Journal*, 26(2), 167–178.

- Xu, H., Yuan, X. D., Shen, B. D., Han, J., Lv, Q. Y., Dai, L., Lin, M. G., Yu, C., Bai, J. X., & Yuan, H. L. (2013). Development of poly(N-isopropylacrylamide)/alginate copolymer hydrogel-grafted fabrics embedding of berberine nanosuspension for the infected wound treatment. *Journal of Biomaterials Applications*
- Xu, W., Gao, Q., Xu, Y., Wu, D., & Sun, Y. (2009). pH-Controlled drug release from mesoporous silica tablets coated with hydroxypropyl methylcellulose phthalate. *Materials Research Bulletin*, 44(3), 606–612.
- Xu, Y., Dong, Q., Qiu, H., Cong, R., & Ding, K. (2010). Structural characterization of an arabinogalactan from *Platycodon grandiflorum* roots and antiangiogenic activity of its sulfated derivative. *Biomacromolecules*, 11(10), 2558–2566.
- Yang, J.-S., Xie, Y.-J., & He, W. (2011). Research progress on chemical modification of alginate: A review. *Carbohydrate Polymers*, 84(1), 33–39.
- Yang, L., & Zhang, L.-M. (2009). Chemical structural and chain conformational characterization of some bioactive polysaccharides isolated from natural sources. *Carbohydrate Polymers*, 76(3), 349–361.
- Yao, K. (2012). *Chitosan-based hydrogels functions and applications* (online resource (x, 511 p.)). Boca Raton, FL: CRC Press1.
- Yu, K. W., Kiyohara, H., Matsumoto, T., Yang, H. C., & Yamada, H. (2001). Characterization of pectic polysaccharides having intestinal immune system modulating activity from rhizomes of *Atractylodes lancea* DC. *Carbohydrate Polymers*, 46(2), 125–134.
- Zambare, V. P., & Christopher, L. P. (2012). Biopharmaceutical potential of lichens. *Pharmaceutical Biology*, 50(6), 778–798.
- Zhang, F., Walcott, B., Zhou, D., Gustchina, A., Lasanajak, Y., Smith, D. F., Ferreira, R. S., Correia, M. T., Paiva, P. M., Bovin, N. V., Wlodawer, A., Oliva, M. L., & Linhardt, R. J. (2013a). Structural studies of the interaction of *Crataeva tapia* bark protein with heparin and other glycosaminoglycans. *Biochemistry*, 52(12), 2148–2156.
- Zhang, J., Jiang, N., Dang, Z., Elder, T., & Ragauskas, A. (2008). Oxidation and sulfonation of cellulose. *Cellulose*, 15(3), 489–496.
- Zhang, J., Xia, W., Liu, P., Cheng, Q., Tahirou, T., Gu, W., & Li, B. (2010). Chitosan modification and pharmaceutical/biomedical applications. *Marine Drugs*, 8(7), 1962–1987.
- Zhang, N., Wardwell, P. R., & Bader, R. A. (2013b). Polysaccharide-based micelles for drug delivery. *Pharmaceutics*, 5(2), 329–352.
- Zhang, Z., Zhang, Q., Wang, J., Song, H., Zhang, H., & Niu, X. (2010). Regioselective syntheses of sulfated porphyrans from *Porphyra haitanensis* and their antioxidant and anticoagulant activities in vitro. *Carbohydrate Polymers*, 79(4), 1124–1129.
- Zhu, H., Srivastava, R., & McShane, M. J. (2005). Spontaneous loading of positively charged macromolecules into alginate-templated polyelectrolyte multilayer microcapsules. *Biomacromolecules*, 6(4), 2221–2228.
- Zhu, L., Kumar, V., & Banker, G. S. (2001). Examination of oxidized cellulose as a macromolecular prodrug carrier: Preparation and characterization of an oxidized cellulose-phenylpropanolamine conjugate. *International Journal of Pharmaceutics*, 223(1–2), 35–47.
- Zimnitsky, D. S., Yurkshtovich, T. L., & Bychkovsky, P. M. (2004). Synthesis and characterization of oxidized cellulose. *Journal of Polymer Science Part A: Polymer Chemistry*, 42(19), 4785–4791.
- Zou, X. H., Foong, W. C., Cao, T., Bay, B. H., Ouyang, H. W., & Yip, G. W. (2004). Chondroitin sulfate in palatal wound healing. *Journal of Dental Research*, 83(11), 880–885.